In The Name of God

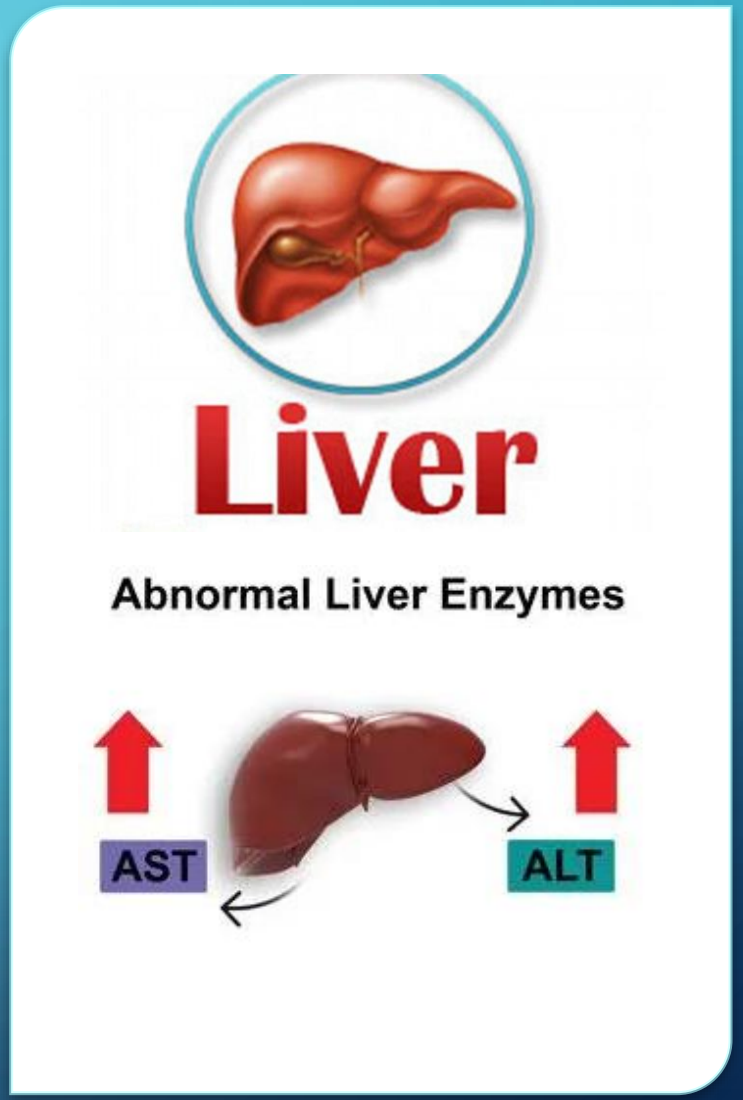
Approach to the child with liver transeaminase elevation

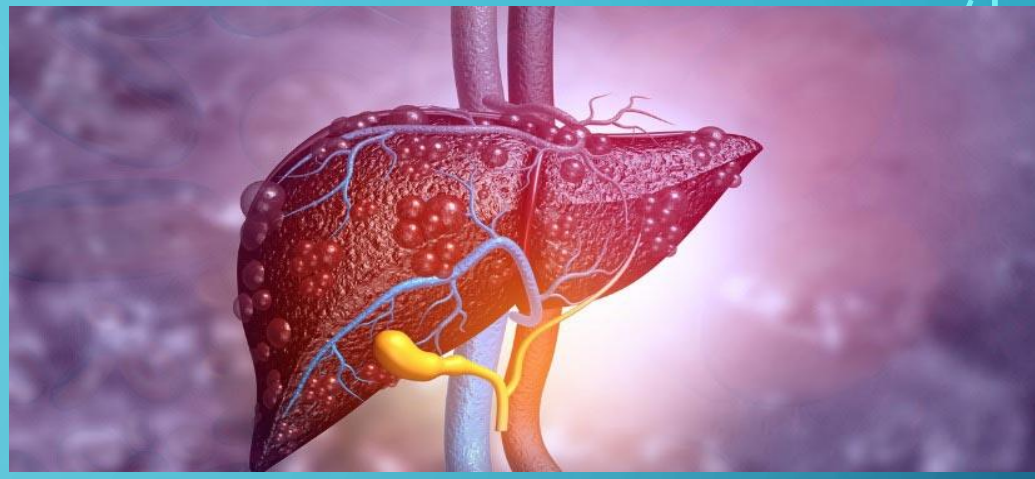
Sanaz Mehrabani

Associate Professor

Babol University Of Medical Sciences

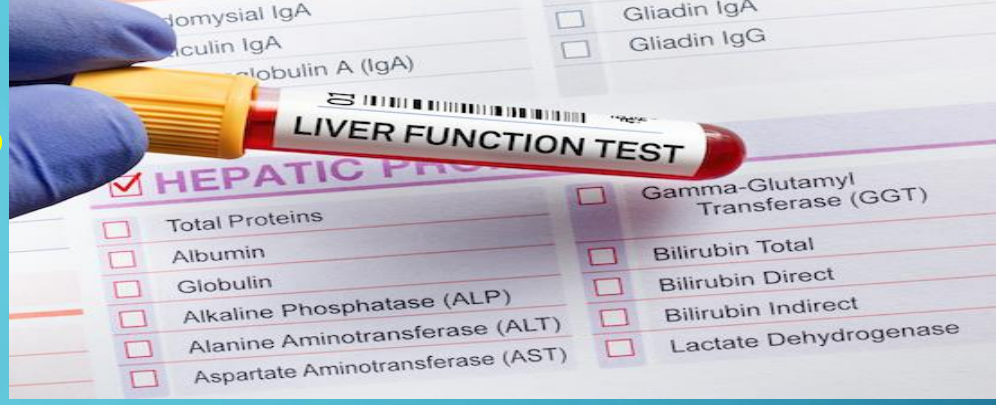
- **Liver enzymes** — Liver enzymes that are commonly measured in the serum include:
- Serum aminotransferases: alanine aminotransferase (ALT, formerly called SGPT or serum glutamic pyruvic transaminase) and aspartate aminotransferase (AST, formerly called SGOT or serum glutamic oxaloacetate transaminase)
- Alkaline phosphatase
- Gamma-glutamyl transpeptidase (GGT)
- 5'-nucleotidase
- Lactate dehydrogenase (LDH)
- **Aminotransferases** — In adults, normal ALT levels range from 29 to 33 units/L for males and 19 to 25 units/L for females. Levels above these values should be assessed for underlying liver disease . In children, median ALT levels range from 17 to 21 units/L in boys and 14 to 20 units/L in girls, with the 97th percentile (commonly used as a cutoff value) of 29 to 38 and 24 to 32 units/L, respectively .Also above 25IU/L for boys and above 22IU/L for girls.(infant 60,55)





- Elevations of liver enzymes often reflect damage to the liver or biliary obstruction
- An abnormal serum albumin or prothrombin time may be seen in impaired hepatic synthetic function.
- The serum bilirubin in part measures the liver's ability to detoxify metabolites and transport organic anions into bile.
- AST(both in cytosolic and mitochondrial isoenzymes) is present in the liver and other organs including cardiac muscle, skeletal muscle, kidney, pancreas,lung,leukocyte ,red blood cells and brain. In children, levels decline with age, more so in girls than boys after age 11.
- ALT(cytosolic enzyme) is present primarily in the liver,lesser in skeletal muscle and thus is a more specific marker of hepatocellular cell injury. ALT levels correlate with the degree of abdominal adiposity

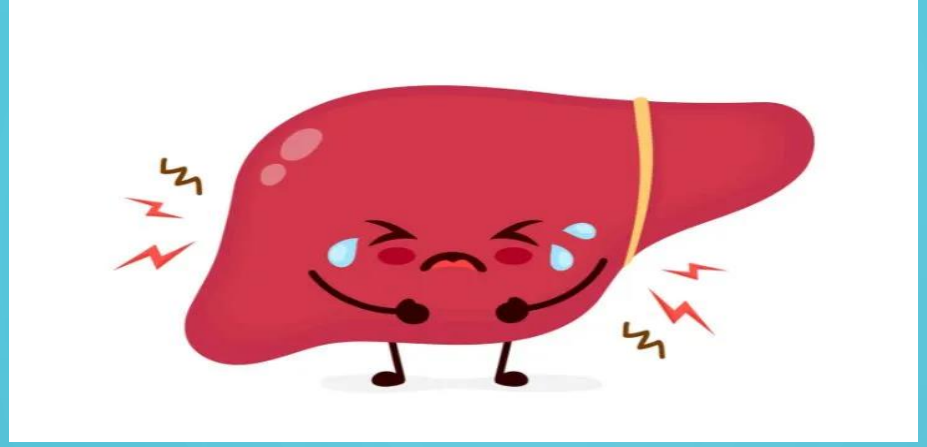
Patterns Of Liver Test Abnormalities



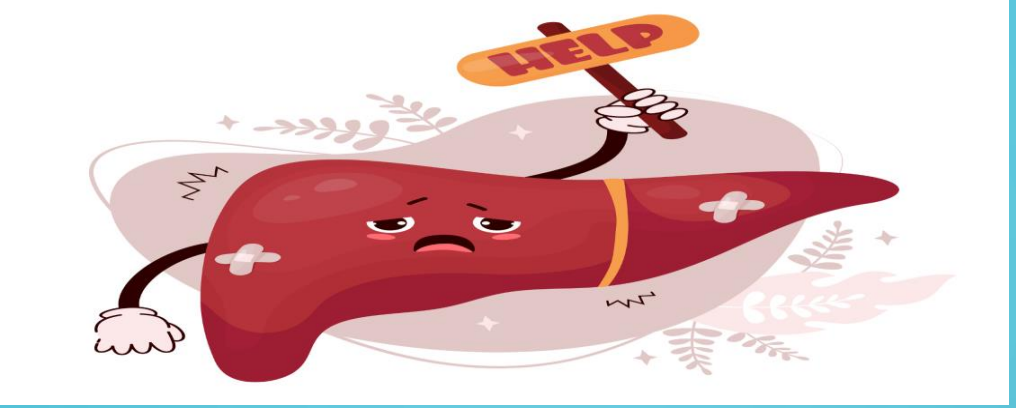
- **Hepatocellular pattern:**
- Disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase
- Serum bilirubin may be elevated
- Tests of synthetic function may be abnormal
- **Cholestatic pattern:**
- Disproportionate elevation in the alkaline phosphatase compared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

Patterns of liver test abnormalities

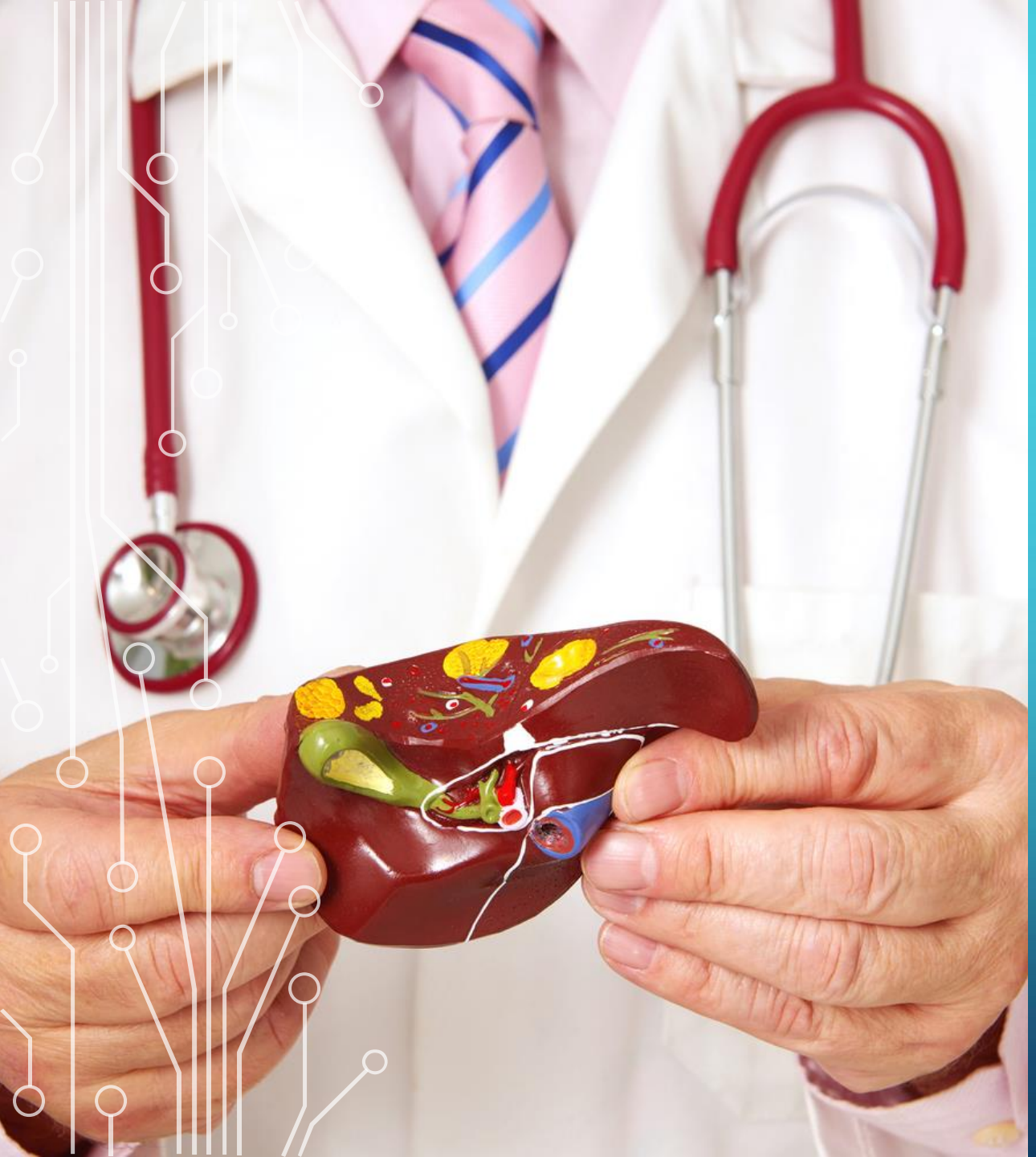
- R VALUE(R FACTOR)=(ALT/ULN ALT)/(ALP/ULN ALP)
- R VALUE≥5: hepatocellular injury
- >2to <5:mixed pattern
- ≤2:cholestatic injury
- Liver abnormality may present less than 6 weeks(acute),sixweeks to six months(subacute),more than six months(chronic)



- **AST to ALT ratio** — Most causes of hepatocellular injury are associated with a serum AST level that is lower than the ALT.
- An AST to ALT ratio of 2:1 or greater is suggestive of alcoholic liver disease, particularly in the setting of an elevated gamma-glutamyl
- The AST to ALT ratio is occasionally elevated in an alcoholic liver disease pattern in patients with nonalcoholic steatohepatitis,metabolic disease,echovirus infection
- And it is frequently elevated (although not greater than two) in patients with hepatitis C who have developed cirrhosis.
- patients with Wilson disease or cirrhosis due to viral hepatitis may have an AST that is greater than the ALT, although in patients with cirrhosis the ratio typically is not greater than two.
- Hemolysis(difficult venipuncture),acute rhabdomyolysis(viral infection),myopathic or myocardial,recent activity ,serum cpk,LDH and haptoglobin for etiology.



- Alcoholic fatty liver disease: AST <8 times the upper limit of normal; ALT <5 times the upper limit of normal.
- Nonalcoholic fatty liver disease: AST and ALT <4 times the upper limit of normal.
- Acute viral hepatitis or toxin-related hepatitis with jaundice: AST and ALT >25 times the upper limit of normal.
- Ischemic hepatitis (ischemic hepatopathy, shock liver, hypoxic hepatitis): AST and ALT >50 times the upper limit of normal (in addition the lactate dehydrogenase is often markedly elevated).
- Chronic hepatitis C virus infection: Wide variability, typically normal to less than twice the upper limit of normal, rarely more than 10 times the upper limit of normal.
- Chronic hepatitis B virus infection: Levels vary; the AST and ALT may be normal in inactive carriers, whereas most patients with chronic hepatitis B have mild to moderate elevations (approximately twice the upper limit of normal); with exacerbations, levels are more than 10 times the upper limit of normal.
- In wilson:cooms negatve hemolytic anemia,ALP/BIL<2, in acute liver failure AST/ALT>2.2 and ALP/BIL<4.



Magnitude of AST

And

ALT Elevations

but first recheck

Elevated Serum Aminotransferases

- In the setting of hepatocyte damage, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are released from hepatocytes, leading to increased serum levels. The differential diagnosis for elevated serum aminotransferases is broad and includes viral hepatitis, hepatotoxicity from drugs or toxins, alcoholic and nonalcoholic liver disease, ischemic hepatitis, and malignant infiltration ,metabolic disease, liver trauma, allograft rejection and autoimmune hepatitis.
- The evaluation should take into account the patient's risk factors for liver disease
- (obtaining a history) as well as findings from the physical examination that may point to a particular diagnosis, Subsequent testing is determined based on the information gathered from the history and physical examination as well as the pattern of test abnormalities

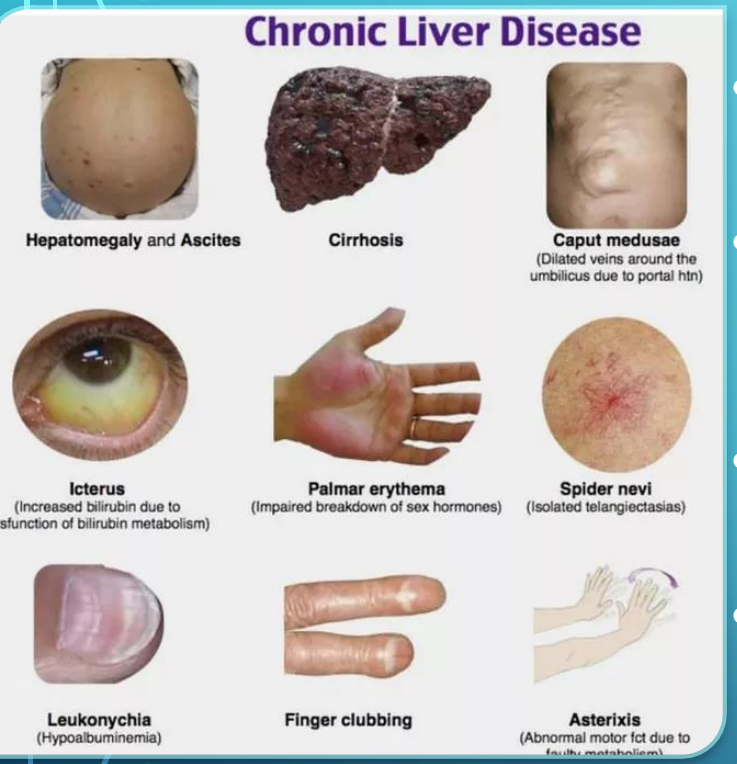
History

- A thorough medical history is central to the evaluation
- should determine if the patient has had exposure to any potential hepatotoxins (including alcohol and medications), is at risk for viral hepatitis, has other disorders that are associated with liver disease, or has symptoms that may be related to the liver disease or a possible predisposing condition.

History

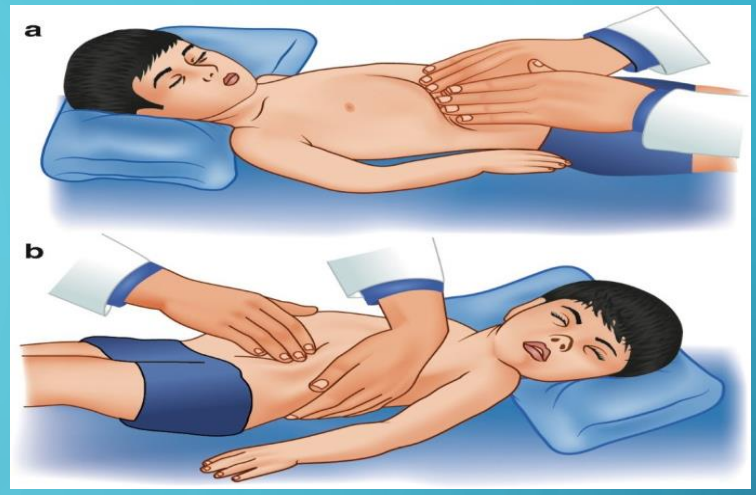
- Drug use is not limited to prescription medications, but also includes over-the-counter medications, herbal and dietary supplements, and illicit drug use
- Risk factors for viral hepatitis include potential parenteral exposures (eg, intravenous drug use, blood transfusion prior to 1992), travel to areas endemic for hepatitis, and exposure to patients with jaundice.
- Hepatitis B and C are transmitted parenterally, whereas hepatitis A and E are transmitted from person to person via a fecal-oral route (often via contaminated food)
- Asked about conditions that are associated with hepatobiliary disease, such as right-sided heart failure (congestive hepatopathy), diabetes mellitus, skin pigmentation, arthritis, hypogonadism and dilated cardiomyopathy (hemochromatosis), and obesity (nonalcoholic fatty liver disease), pregnancy (gallstones), inflammatory bowel disease (primary sclerosing cholangitis, gallstones), early onset emphysema (alpha-1 antitrypsin deficiency), celiac disease, and thyroid disease.
- Finally, patients should be questioned about occupational or recreational exposure to hepatotoxins (eg, mushroom picking). Examples exposures to hepatotoxins include industrial chemicals such as vinyl chloride and the mushrooms *Amanita phalloides* and *Amanita verna*

Physical Examination



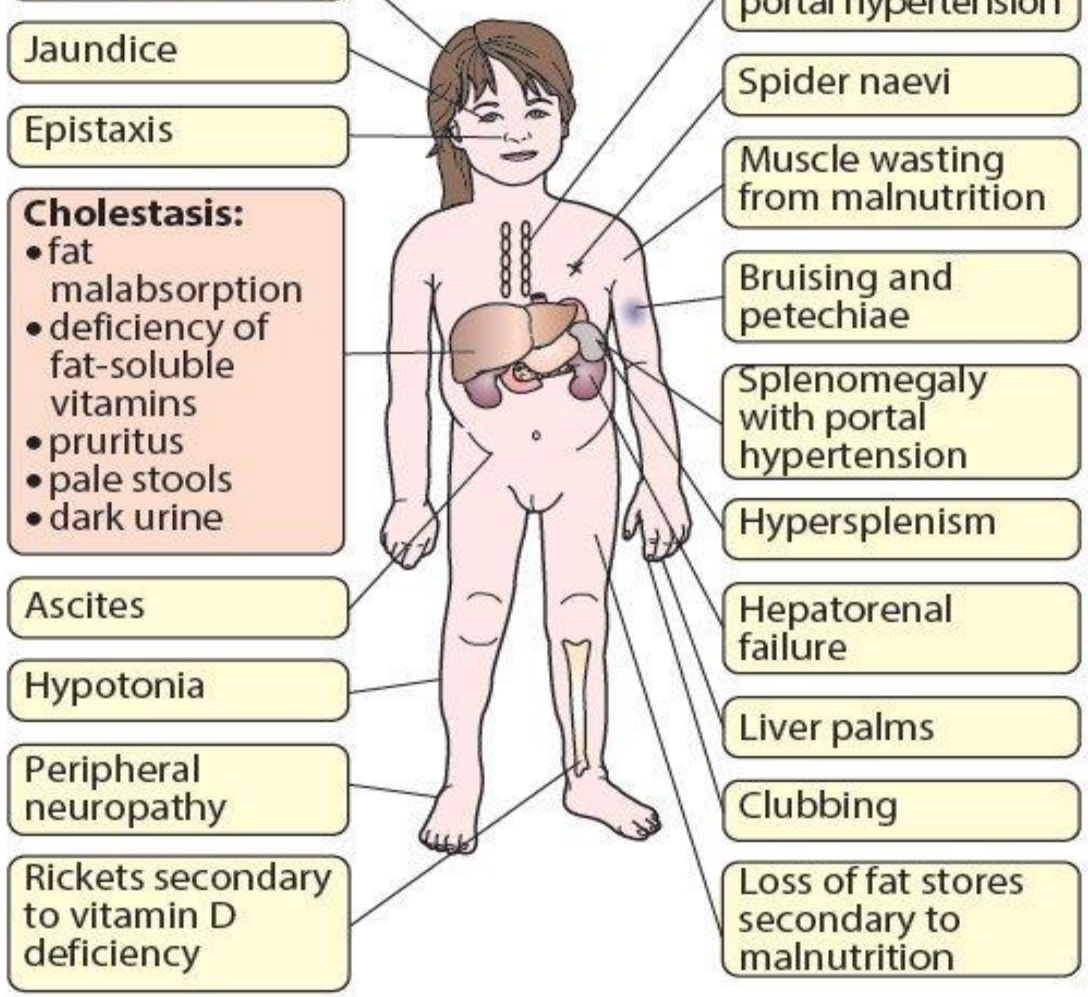
- Temporal and proximal muscle wasting suggest longstanding disease.
- Stigmata of liver disease include spider nevi, palmar erythema, gynecomastia, and caput medusae.
- Ascites or hepatic encephalopathy may be seen in patients with decompensated cirrhosis.
- Dupuytren's contractures, parotid gland enlargement, and testicular atrophy are commonly seen in advanced alcoholic cirrhosis and occasionally in other types of cirrhosis.
- An enlarged left supraclavicular node (Virchow's node) or periumbilical nodule (Sister Mary Joseph's nodule) suggest an abdominal malignancy.
- Increased jugular venous pressure, a sign of right-sided heart failure, suggests hepatic congestion.
- A right pleural effusion, in the absence of clinically apparent ascites, may be seen in advanced cirrhosis
- Neurologic and psychiatric signs and symptoms may be seen in patients with Wilson disease.

Physical Examination



- The abdominal examination should focus on the size and consistency of the liver, the size of the spleen (a palpable spleen is two to threefold enlarged), and an assessment for ascites (usually by determining whether there is a fluid wave, shifting dullness, or bulging of the flanks).
- Patients with cirrhosis may have an enlarged left lobe of the liver (which can be felt below the xiphoid) and an enlarged spleen (which is most easily appreciated with the patient in the right lateral decubitus position).
- A grossly enlarged, hard, nodular liver or an obvious abdominal mass suggests malignancy.
- An enlarged, tender liver could be due to viral or alcoholic hepatitis or, less often, an acutely congested liver secondary to right-sided heart failure or Budd-Chiari syndrome.
- Severe right upper quadrant tenderness with a positive Murphy's sign (respiratory arrest on inspiration while pressing on the right upper quadrant) suggests cholecystitis or, occasionally, ascending cholangitis.
- Ascites in the presence of jaundice suggests either cirrhosis or malignancy with peritoneal spread.

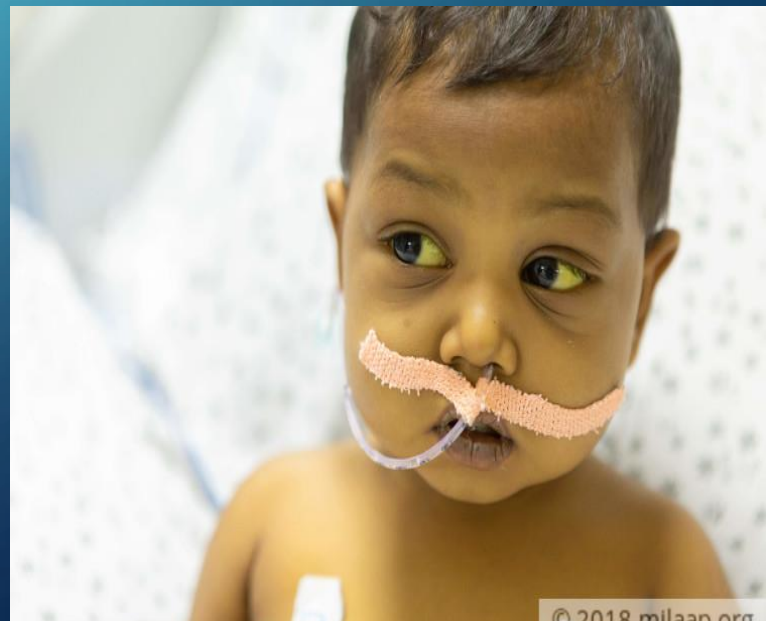
Hepatic dysfunction



Clinical features of liver disease. In addition, these children may have growth failure and developmental delay.

Acute Liver Failure

- Is characterized by acute hepatocellular injury with liver tests typically more than 10 times the upper limit of normal, hepatic encephalopathy, and a prolonged prothrombin time (international normalized ratio greater than or equal to 1.5).
- Rapid decline in aminotransferase with increase in bilirubin and coagulopathy is poor prognosis.



Marked elevation without liver failure

- Patients with marked or severe elevations in their aminotransferase levels (approximately 15 times the upper limit of normal or higher) often have acute hepatitis, although in some cases, there may be underlying chronic liver disease (eg, Wilson disease or an acute exacerbation of hepatitis B virus).
- Massive elevations in aminotransferases (>5,000 U/L) are usually due to ischemic or drug-induced hepatitis.
- Other causes of massive elevations in AST include rhabdomyolysis and heat stroke.
- There is a poor correlation between serum elevation of transaminase and extent of liver necrosis in liver biopsy.

Marked Elevations In Serum Aminotransferase Levels May Be Seen With:

- Acetaminophen (paracetamol) toxicity
- Idiosyncratic drug reactions
- Acute viral hepatitis (hepatitis A, B, C, D, E; herpes simplex virus; varicella zoster virus; Epstein-Barr virus; cytomegalovirus [CMV]); other viral infections; or an acute exacerbation of chronic viral hepatitis (hepatitis B)
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson disease
- Ischemic hepatitis
- Budd-Chiari syndrome
- Sinusoidal obstruction syndrome (veno-occlusive disease)

Marked elevations in serum aminotransferase levels may be seen with:

- HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and occasionally acute fatty liver of pregnancy
- Malignant infiltration (most often breast cancer, small cell lung cancer, lymphoma, melanoma, or myeloma)
- Partial hepatectomy
- Toxin exposure, including mushroom poisoning
- Sepsis
- Heat stroke
- Muscle disorders (acquired muscle disorders [eg, polymyositis], seizures, and heavy exercise [eg, long distance running]

Evaluation of markedly elevated aminotransferases

- Acetaminophen level
- Toxicology screen
- Acute viral hepatitis serologies
- IgM anti-hepatitis A virus.
- Hepatitis B surface antigen (HBsAg), IgM anti-hepatitis B core antigen (anti-HBc), antibody to HBsAg.
- Anti-hepatitis C virus antibody (HCV), hepatitis C viral RNA.
- In some cases (based on patient history and risk factors): anti-herpes simplex virus antibodies, anti-varicella zoster antibodies, anti-CMV antibodies, CMV antigen, and, for Epstein-Barr virus, heterophile antibody.
- Serum pregnancy test in women of childbearing potential who are not already known to be pregnant
- Autoimmune markers (antinuclear antibodies, anti-smooth muscle antibodies, anti-liver/kidney microsomal antibodies type 1, IgG)
- Transabdominal ultrasonography with Doppler imaging to look for evidence of vascular occlusion (eg, Budd-Chiari syndrome)

Evaluation of markedly elevated aminotransferases

- Ceruloplasmin level and urinary copper quantitation in patients suspected of having Wilson disease.
- Hepatitis D virus antibodies in patients with acute or chronic hepatitis B.
- Hepatitis E virus antibodies in patients who live in or travel to areas endemic for hepatitis E, such as Asia, Africa, the Middle East, and Central America, or in patients who are pregnant (because of the high rates of acute liver failure in pregnant women with hepatitis E).
- Urinalysis to look for proteinuria in women who are pregnant.
- Serum creatinine kinase or aldolase in patients with risk factors for or symptoms of muscle disorders.

Evaluation of markedly elevated aminotransferases

- The above testing is negative, we typically proceed with a liver biopsy if the acute elevation of the serum aminotransferases fails to resolve or decline, or if the patient appears to be developing acute liver failure.
- If the elevation is less than five times the upper limit of normal and the patient appears well, we may follow the patient expectantly, checking liver tests every three to six months.

Mild to moderate elevations of the serum aminotransferases

- Mild to moderate elevations of the serum aminotransferases (less than 15 times the upper limit of normal) are often seen with chronic liver disease, although transient elevations may also be seen in patients with mild hepatic insults (eg, intake of nontoxic doses of acetaminophen).

Conditions associated with mild to moderate serum aminotransferase elevations include

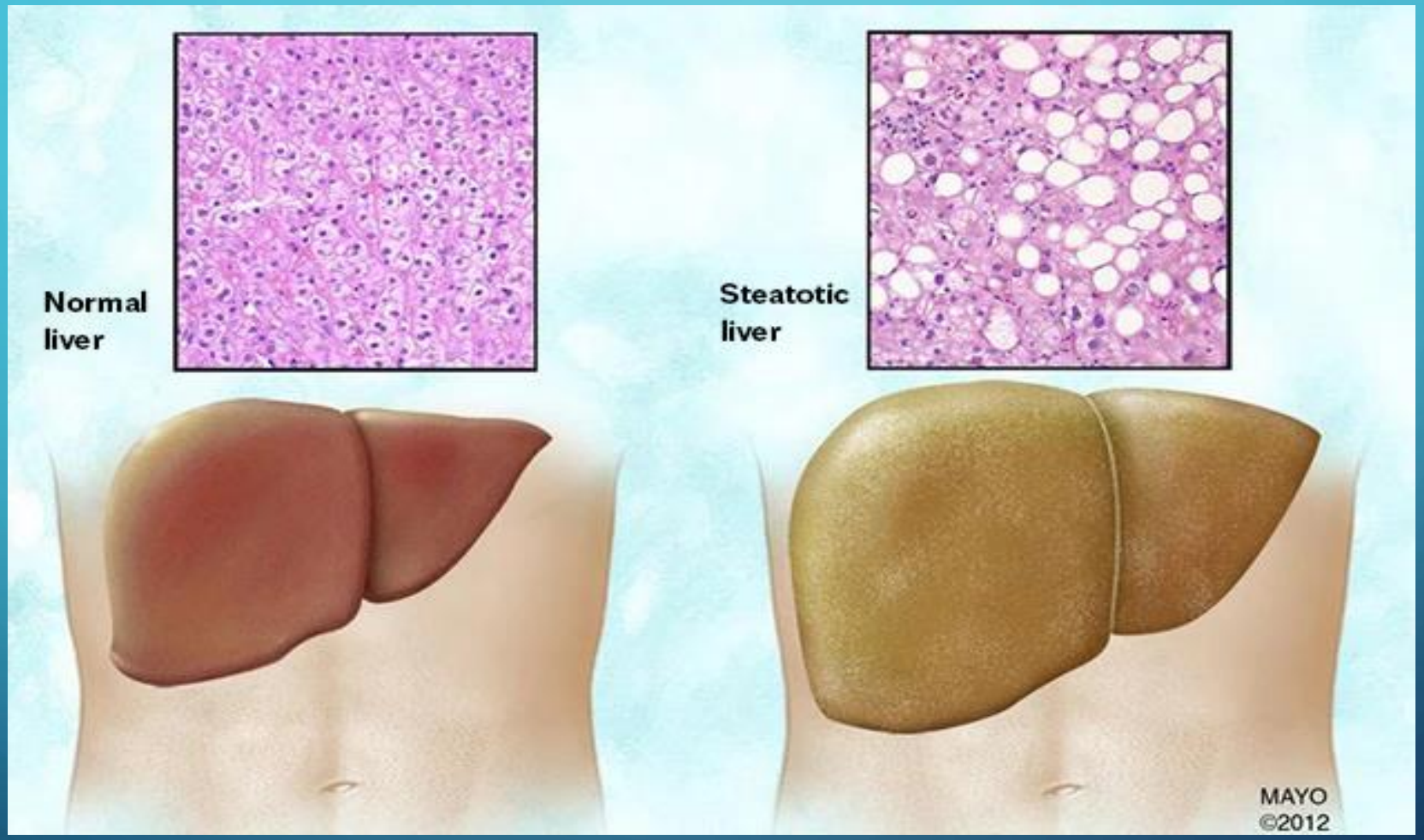
- Medication use
- Chronic viral hepatitis (hepatitis B, C, D)
- Alcoholic liver disease
- Hemochromatosis
- Nonalcoholic fatty liver disease
- Autoimmune hepatitis
- Wilson disease
- Alpha-1 antitrypsin deficiency
- Congestive hepatopathy

Conditions associated with mild to moderate serum aminotransferase elevations include

- Adult bile ductopenia
- Malignant infiltration (most often breast cancer, small cell lung cancer, lymphoma, melanoma, or myeloma)
- Muscle disorders (eg, subclinical inborn errors of muscle metabolism)
- Thyroid disorders
- Celiac disease
- Adrenal insufficiency
- Anorexia nervosa
- Macro-AST (moderate elevations in plasma AST levels due to the presence AST-immunoglobulin complexes, usually IgG)

Evaluation of mildly or moderately elevated aminotransferases

- We typically start the evaluation with the following:
- Hepatitis B: HBsAg, antibody to HBsAg, anti-HBc.
- Hepatitis C: Anti-HCV.
- Hemochromatosis: Serum iron and total iron binding capacity (TIBC) with calculation of transferrin saturation (serum iron/TIBC). A transferrin saturation greater than 45 percent warrants obtaining a serum ferritin. Ferritin is less useful as an initial test because it is an acute phase reactant and therefore less specific than the transferrin saturation. A serum ferritin concentration of greater than 400 ng/mL (900 pmol/L) in men and 300 ng/mL (675 pmol/L) in women further supports (but does not confirm) the diagnosis of hemochromatosis
- Nonalcoholic fatty liver disease: The initial evaluation is radiologic imaging, usually ultrasonography, or possibly computed tomography (CT) or magnetic resonance imaging (MRI). Ultrasonography has a lower sensitivity than CT or MRI but is less expensive.


Normal liver
Steatotic liver
MAYO ©2012

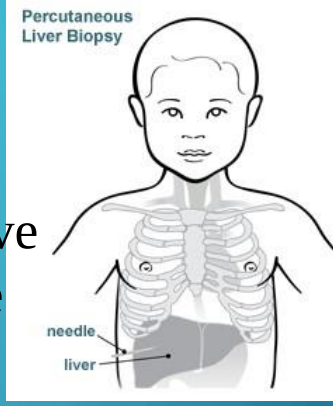
Evaluation of mildly or moderately elevated aminotransferases

- If the initial evaluation fails to identify a likely source of the aminotransferase elevation, we test for the following:
- Autoimmune hepatitis: Antinuclear antibodies, anti-smooth muscle antibodies, and anti-liver/kidney microsomal antibodies, IgG
- Wilson disease: Serum ceruloplasmin, evaluation for Kaiser-Fleisher rings,
- Alpha-1 antitrypsin deficiency: Serum alpha-1 antitrypsin level; if indicated, alpha-1 antitrypsin phenotyping
- Thyroid disorders: Thyroid-stimulating hormone, free T4 concentration, free T3 concentration
- Celiac disease: Antibody screening with serum tissue transglutaminase antibodies

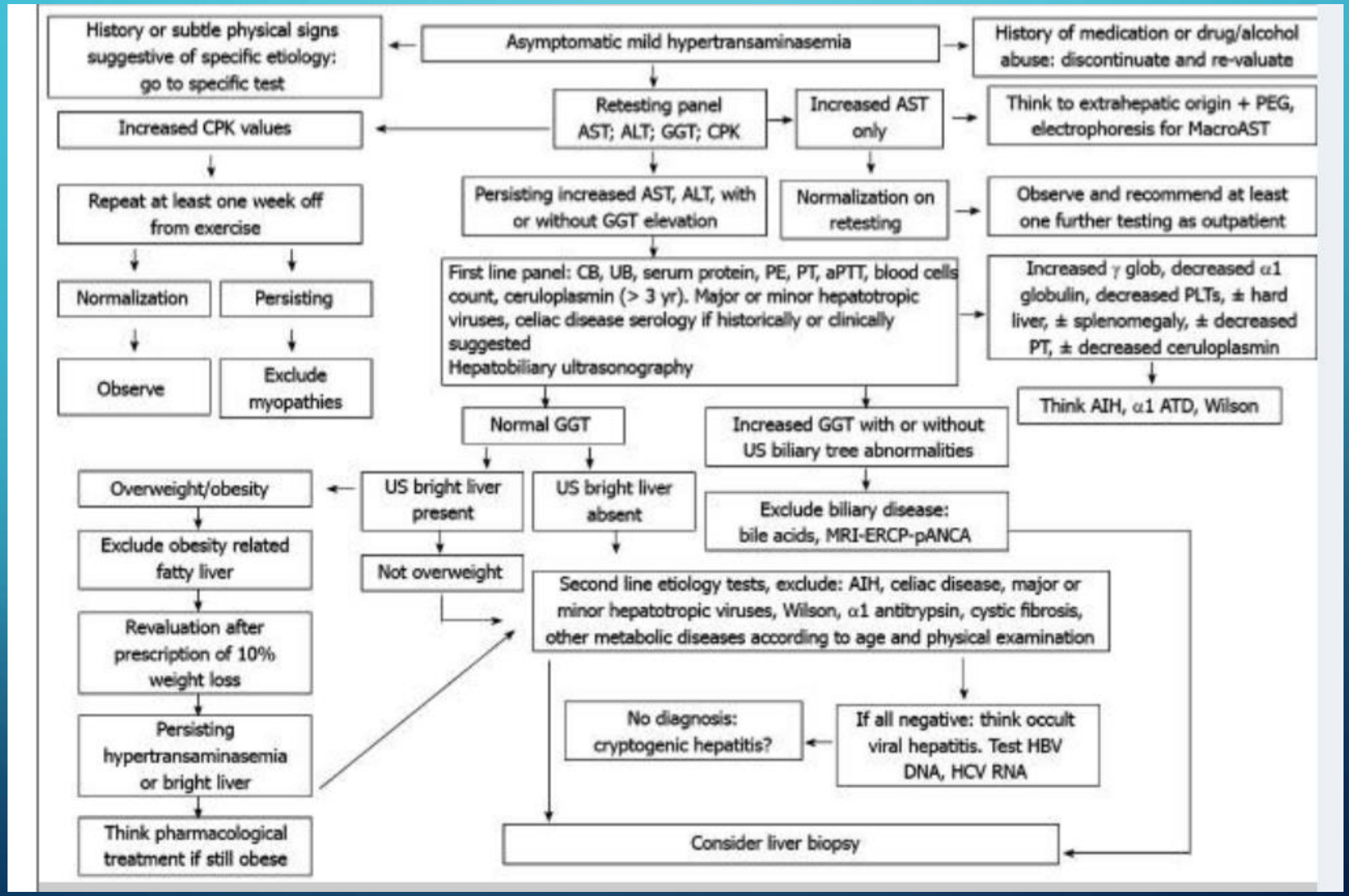
Evaluation of mildly or moderately elevated aminotransferases

- If the source of the liver test abnormalities is still unclear, we test for the following:
- Adrenal insufficiency (in patients with symptoms associated with adrenal insufficiency, such as chronic malaise, anorexia, or weight loss): 8 AM serum cortisol and plasma corticotropin (ACTH), and a high-dose ACTH stimulation test
- Muscle disorders (in patients with symptoms such exercise intolerance, muscle pain, or muscle weakness): Creatinine kinase or aldolase
- A liver biopsy is often considered in patients in whom all of the above testing has been unrevealing
- However, in some settings, the best course may be expectant observation.

Suggest



- We suggest expectant observation in patients in whom the ALT and AST levels are less than five times the upper limit of normal and no chronic liver condition has been identified by the above noninvasive testing.
- We use a conservative estimate for the upper limit of normal for aminotransferases (approximately 33 units/L for men and 25 units/L for women). In such patients, we will follow their liver biochemical and function tests every six months.
- This approach was supported by a preliminary study in which expectant clinical follow-up was found to be the most cost-effective strategy for managing asymptomatic patients with negative viral, metabolic, and autoimmune markers and chronically elevated aminotransferases.
- A second small study also found that biopsy results rarely affected the management of such patients .
- We suggest a liver biopsy in patients in whom the ALT and AST are persistently greater than twice the upper limit of normal, particularly if noninvasive testing suggests that advanced liver fibrosis is unlikely.
- Occasionally, the biopsy will provide an unsuspected diagnosis or lead to a change in management.
- In most cases, however, the biopsy proves reassuring to the patient and clinician by confirming that there is no evidence of serious or advanced liver disease.


Asymptomatic mild hypertransaminasemia
History or subtle physical signs suggestive of specific etiology: go to specific test
History of medication or drug/alcohol abuse: discontinuate and re-valuate
Retesting panel AST; ALT; GGT; CPK
Increased AST only
Think to extrahepatic origin + PEG, electrophoresis for MacroAST
Increased CPK values
Repeat at least one week off from exercise
Normalization
Persisting
Observe
Exclude myopathies
Persisting increased AST, ALT, with or without GGT elevation
Normalization on retesting
Observe and recommend at least one further testing as outpatient
First line panel: CB, UB, serum protein, PE, PT, aPTT, blood cells count, ceruloplasmin (> 3 yr). Major or minor hepatotropic viruses, celiac disease serology if historically or clinically suggested
Hepatobiliary ultrasonography
Increased γ glob, decreased α1 globulin, decreased PLTs, ± hard liver, ± splenomegaly, ± decreased PT, ± decreased ceruloplasmin
Think AIH, α1 ATD, Wilson
Normal GGT
Increased GGT with or without US biliary tree abnormalities
Overweight/obesity
US bright liver present
US bright liver absent
Exclude biliary disease: bile acids, MRI-ERCP-pANCA
Exclude obesity related fatty liver
Not overweight
Second line etiology tests, exclude: AIH, celiac disease, major or minor hepatotropic viruses, Wilson, α1 antitrypsin, cystic fibrosis, other metabolic diseases according to age and physical examination
Revaluation after prescription of 10% weight loss
Persisting hypertransaminasemia or bright liver
No diagnosis: cryptogenic hepatitis?
If all negative: think occult viral hepatitis. Test HBV DNA, HCV RNA
Think pharmacological treatment if still obese
Consider liver biopsy

With Thanks