

Approach to the Patient with Abnormal Liver Tests

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What do we understand by LFTs?

- We usually refer to the measurement of bilirubin, AST, ALT, GGT, and Alkaline phosphatase → Liver Tests.
- They do not measure liver function.
- They detect liver cell damage or interference with bile flow.
- LFTs: PT, albumin, F-V, F-VII, and others rarely used.

Why do we use them?

- They provide a noninvasive method of screening for the presence of liver dysfunction.
- The pattern can help to recognize the general type of liver disorder.
- They allow us to assess the severity of liver dysfunction, and to predict outcome.
- Allow to follow the course of liver diseases.

Limitations

- They are not specific for liver dysfunction.
- They seldom provide a specific diagnosis.
- No one enable to accurately assess the total functional capacity of the liver.

Bilirubin

- It is a breakdown product of heme-containing proteins, mainly hemoglobin.
- It is conjugated in the liver to form conjugated-Bb, aka direct-Bb.
- Conjugated Bb is then transported into the canaliculi and excreted in the bile.
- Up to 70% of the Bb is direct and up to 30% is indirect.

Bilirubin

- If more than 80% of the Bb is indirect:
“**unconjugated hyperbilirubinemia**”
and suggests hemolysis or Gilbert’s.
- If more than 50% of the Bb is direct:
“**conjugated hyperbilirubinemia**” and
indicates hepatocellular dysfunction or
cholestasis.

Bilirubin

- Bilirubin level represents a balance between production and hepatic removal.
- Hyperbilirubinemia may result from:
 - Overproduction (e.g. hemolysis)
 - Impaired uptake, conjugation, or excretion.
 - Regurgitation of unconjugated or conjugated bilirubin from damaged hepatocytes or bile ducts.

Bilirubin

- It is not a sensitive indicator of hepatic dysfunction.
- It may not accurately reflect the degree of liver damage.
- HyperBb may not be detected in moderate to severe hepatic dysfunction or in partially or briefly obstructed common bile duct.

Bilirubin

- The height of the total Bb is seldom of value in specifying the cause of the jaundice.
- However:
 - In common bile duct obstruction it is unusual to be >15 mg/dl. It is usually <6 mg/dl.
 - If $>25-30$ mg/dl, extrahepatic cholestasis is unlikely.
 - Uncomplicated hemolysis and Gilbert's seldom cause values >6 mg/dl.
 - The highest values are seen in sepsis (>50 mg/dl) and drug-induced cholestasis.

Liver Enzymes

- Serum enzymes tests can be grouped into two categories:
 - Enzymes whose elevation reflects generalized hepatocellular damage.
 - Enzymes whose elevation primarily reflects cholestasis.

Aminotransferases

- They are sensitive indicators of liver cell injury.
- They are most helpful in recognizing acute hepatocellular diseases (hepatitis).
- We basically measure two types of aminotransferases:
 - Alanine aminotransferase or ALT (SGPT).
 - Aspartate aminotransferase or AST (SGOT).

Aminotransferases

- The organ source of these enzymes are different:
 - AST is present in decreasing order of concentration in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes.
 - Because of its wide tissue distribution, elevated AST levels have low specificity for any single disease.
 - ALT is present almost exclusively in the liver, therefore it is a better index of liver cell injury.

Aminotransferases

- ALT is located in the cytosol.
- AST occurs in the cytosol (20%) and the mitochondria (80%) but normal serum activity is mainly related to the cytosol.
- Both require pyridoxine (vit B₆) as cofactor but ALT is more sensitive.
- AST is cleared from serum faster than ALT: 17±5 hours vs. 47±10 hours

Aminotransferases

- They differ in their localization within the liver acinus: ALT mostly periportal; AST is localized throughout the liver.
- They increase when there is damage to or destruction of tissue rich in aminotransferases or to changes in cell membrane permeability which allow them to leak into the serum.
- They are typically elevated in all sort of liver disorders, acute and chronic.

Aminotransferases

- Elevations up to 8 ULN are nonspecific and may be found in any liver disorder.
- The highest elevations occur in disorders associated with extensive hepatocellular injury.

Aminotransferases

- The degree of elevation does not correlate with the extent of damage, so it has no prognostic value.
- Patients with normal levels may have significant liver damage.

Aminotransferases:

Alcoholic Liver Disease

- Alcoholic hepatitis
 - The damage is primarily in the mitochondria, and thus the AST increase is higher than ALT.
 - Patients with alcoholic liver disease have pyridoxine deficiency, and ALT is more sensitive to its deficiency, therefore ALT level tends to be lower or normal.
 - The AST increase is usually not greater than 300 U/L.

Aminotransferases: Alcoholic Liver Disease

- Alcoholic hepatitis
 - An AST:ALT ratio >2.0 suggests alcoholic liver disease and a ratio >3 it is highly suspicious.
 - This ratio is maintained even in cases where alcoholic patients develop acute hepatitis.
 - The AST:ALT ratio is less useful in chronic liver disease.

Aminotransferases

- Choledocholithiasis:
 - AST increase is the earliest abnormality and is usually not >5-fold.
 - In the presence of cholangitis the increase can be up to 10-fold.
 - In acute bile duct obstruction it may reach the thousands and be confused with hepatitis.
 - AST increase is transient, reach a peak within 24-48h and returns to normal within 72 hours.

Aminotransferases

- Viral Hepatitis:
 - They steadily increase and peak in the low thousands range within 7-14 days.
 - The elevation of Bb usually lags behind the rise in aminotransferases by about a week.
 - They usually return to normal in about 6 weeks.
 - Hepatitis C is associated with fluctuations in ALT and AST.

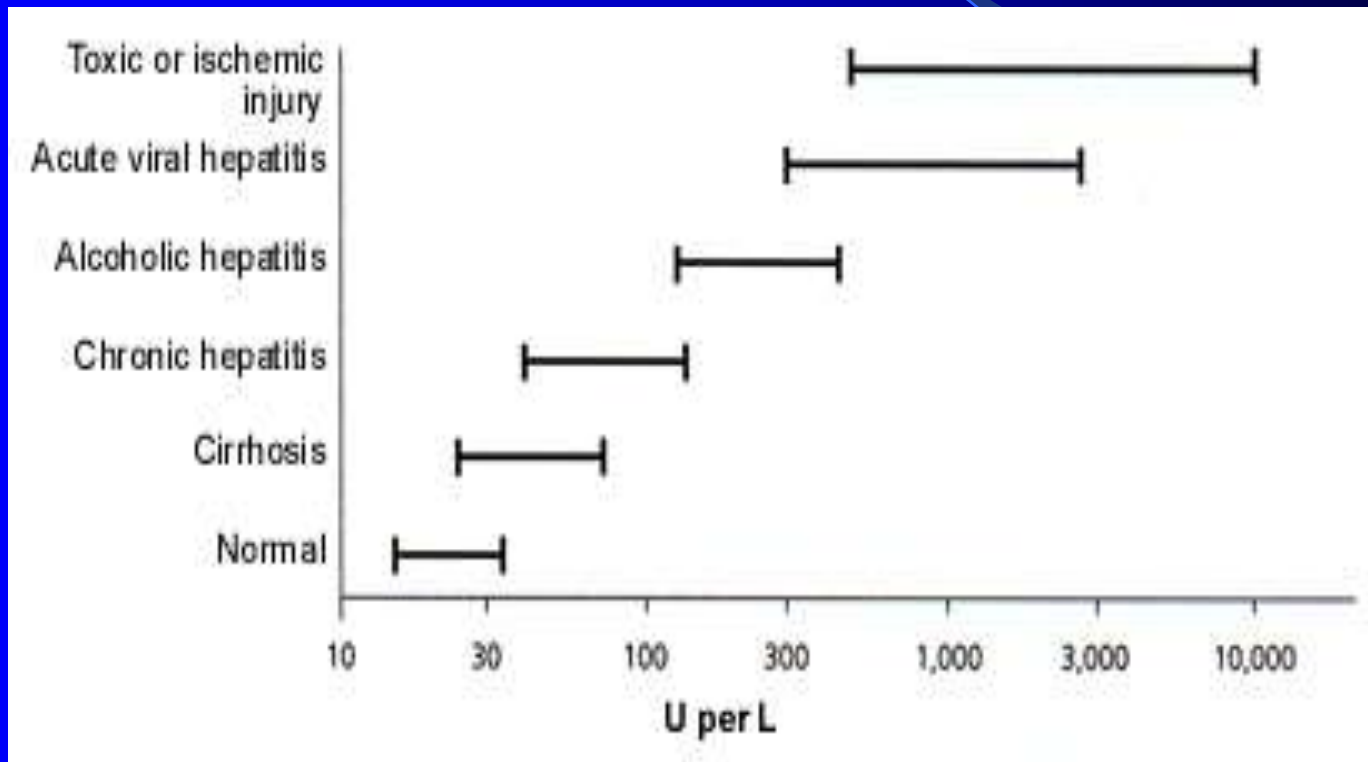
Aminotransferases

- Ischemic Hepatitis (*i.e.* cardiac failure, shock, hypotension, cocaine, etc):
 - They abruptly increase within 24h.
 - They may be greater than 10,000 U/L.
 - They rapidly return to normal within a week.
- Increases $>10,000$ U/L can also be seen with acetaminophen overdose and in *Herpes simplex* hepatitis.

Aminotransferases

- In drug-induced hepatitis they tend to have the same behavior as in viral hepatitis.
- Many medications cause an increase in AST.
- NASH, hyper- and hypothyroidism can also cause increased transaminases.
- Low AST values may be seen in patients with uremia and they can be falsely low after dialysis.

Typical AST or ALT Values in Disease



Alkaline Phosphatase

- It is present in the liver, bone, placenta, intestine, and kidneys.
- There are several isoenzymes.
- More than 80% of circulating ALP is from the liver and bone.
- Liver ALP is associated with the sinusoidal and canalicular membranes of the hepatocyte and biliary epithelium.

Alkaline Phosphatase

- They should (must) be measured fasting.
- Its half-life is 7 days and its clearance from serum is independent of the functional capacity of the liver or the patency of the bile ducts.

Alkaline Phosphatase

- The response to obstruction or bile injury is an increased synthesis of ALP.
- This can result even if the obstruction is in a few small bile ducts and insufficient to cause an increase in Bb.

Alkaline Phosphatase

- When ALP is elevated it indicates cholestasis at some level:
 - Diffusely within the liver or intrahepatic.
 - Extrahepatic (gallstones, tumors).
 - Localized within the liver (tumors).
 - Patchy involvement within the liver (granulomatous disease).
- The extent of the elevation does not distinguish among them.

Alkaline Phosphatase

- If ALP fractioning is not available, GGT helps to determine its liver origin.
- ALP level can also be increased in:
 - Hyperthyroidism
 - Cardiac failure
 - Lymphoma or other infiltrative diseases
 - Renal cell carcinoma

Alkaline Phosphatase

- When interpreting the values, keep in mind that:
 - Children may have levels up to 3 ULN.
 - In pregnant women can be increased up to 2 ULN.
 - Not always represent liver disease.
 - Its level may be low in Wilson's disease complicated by hemolysis.

Alkaline Phosphatase

- When ALP is increased disproportionately to the Bb level – Bb <1 mg/dl and ALP $>1,000$ U/L – suggestive diagnosis are granulomatous or infiltrative diseases:
 - Lymphoma
 - TB
 - Sarcoidosis
 - Fungal infections
 - Tumors (primary, metastasis, benign or malignant)
 - PBC and PSC
 - Extrahepatic biliary obstruction

Alkaline Phosphatase

- Causes of intrahepatic cholestasis include PBC, sepsis, and drugs.
- Typical causes of extrahepatic cholestasis are choledocholithiasis, strictures, tumors.
- ALP levels up to 3 ULN are common in patients with acute hepatocellular disorders.
- Values ≥ 4 ULN suggest some type of cholestasis.

GGT

- Sensitive marker of hepatobiliary disease, but very unspecific.
- Major clinical utility is to exclude a bone source of ALP elevation.
- Half-life is 26 days → it is of limited value as a marker of surreptitious alcohol ingestion.
- It is inducible, so drugs usually elevate it.
- If it is the only abnormality, does not warrant further evaluation.

Common Serum Liver Tests

Liver Chemistry Test	Clinical Implication of Abnormality
ALT	Hepatocellular damage
AST	Hepatocellular damage
Bilirubin	Cholestasis, impaired conjugation, biliary obstruction.
Alkaline phosphatase	Cholestasis, biliary obstruction, biliary injury, or infiltrative disease
Prothrombin time	Synthetic function
Albumin	Synthetic function
GGT	Cholestasis, biliary obstruction
LDH	Hepatocellular damage, not specific for liver disease

Clinical Approach

- **The first step: repeat the test to confirm the result.**
- ***“Rule of thumb”***: confirm each abnormal liver test result with another test:
 - AST with ALT or vice versa.
 - ALP with GGT or fractioning.
 - Albumin with prothrombin.

Clinical Approach

- Bb can be increased in hemolysis and sepsis.
 - In the presence of hemolysis:
 - Reticulocyte count is increased
 - Peripheral smear is usually abnormal
 - LDH is elevated
 - Bb is mainly indirect
 - Haptoglobin is decreased

Clinical Approach

- **Second step: classify the liver disease as:**
 - Hepatocellular
 - Intrahepatic cholestasis
 - Extrahepatic cholestasis

Clinical Approach

- **Third step: correlate the clinical history and physical examination with the pattern of alteration.**
- When taken the history, never forget to ask about medications (prescribed or OTC), illicit drugs, herbs, and nutritional supplements.
- Epidemiological data and past medical history are also important (drug use, promiscuity, travel, previous surgery, age, etc.)

Clinical Approach

- **Fourth step: formulate a differential diagnosis.**

Clinical Approach

- **Fifth step: make a specific diagnosis.**
- This almost always requires additional tests:
 - Serologies.
 - Imaging studies: CT, US, MRI.
 - Invasive procedures: ERCP, PTHC, Biopsy.
 - Other labs: ceruloplasmin, iron studies, etc.

Clinical Approach

Test	Laboratory Study
Viral Hepatitis <ul style="list-style-type: none">• Hepatitis B• Hepatitis C	HBsAg, HBsAb and HBc _{total} Ab HCV Ab with reflex to HCV PCR if (+)
Autoimmune hepatitis	ANA, SMA, AMA, IgG and IgM
Hemochromatosis	Iron studies (TIBC, TS, ferritin) and HFE
Celiac disease	Tissue transglutaminase, Duodenal Bx
Toxicity	Good history
Alcoholic liver disease	Good history, AST:ALT ratio
Wilson's disease	Ceruloplasmin
α 1-antitrypsin deficiency	α 1-antitrypsin phenotype α 1-antitrypsin levels

Clinical Approach

- **Rule-of-thumb:** if the pattern is mainly cholestatic is almost mandatory to demonstrate patency of the biliary tract.
- The initial imaging study of choice is the US/CT: biliary dilatation, focal lesions, gallbladder, ascites, etc.

Clinical Approach

- Whenever transaminases are the main alteration, specially if ALT is persistently elevated, and no matter how high they are, always request HCV and HBV serologies.
- If AST is the only alteration (normal ALT) think about alcohol and extrahepatic diseases (MI, muscle, etc).

Clinical Approach

- If a second determination is normal, always repeat test 3-6 months later.
- If drugs or alcohol are suspected, repeat test 2-8 wks after drug discontinuation or alcohol abstinence.

When to Refer to a Gastroenterologist I

- Unexplained jaundice
- Suspected biliary obstruction
- Severe or fulminant acute hepatitis
- Persisting (≥ 6 months) and unexplained elevation of LFTs
- Unexplained cholestatic liver disease

When to Refer to a Gastroenterologist II

- Cirrhosis for consideration of liver transplantation
- Suspected hereditary hemochromatosis
- Suspected Wilson's disease
- Suspected autoimmune hepatitis
- Chronic hepatitis B or C for consideration of antiviral therapy

Conclusions

- A good history is very important.
- Confirm abnormality.
- Always ask for medications, OTC, herbs, etc.
- Observation is an option in patients that are not acutely ill.



Thank You