KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Blood Chem Impaired Gallbladder and Liver Disease Review

MARKERS OF IMPAIRED LIVER FUNCTION

Marker	Value
ALT	High
AST	High
GGT	High
LDH	High
Alkaline phosphatase	High

AMINOTRANSFERASES (ALT AND AST)

- ALT is a specific indicator of liver damage that is present in the highest amount in the liver.
- AST is present in tissues with high metabolic activity, including liver, heart, and kidney. It's not specific to the liver, but liver dysfunction is the most common cause of elevated AST.
- Elevated aminotransferases typically reflect abnormalities in liver cells or the bile duct.

GAMMA-GLUTAMYL TRANSFERASE (GGT)

- Primarily found in the hepatocytes and biliary epithelium. However, due to its presence in many tissues, it is not specific for liver and gallbladder disease.
- GGT and alkaline phosphatase levels increase in the blood with hepatobiliary obstruction
- Unlike alkaline phosphatase, GGT is not found in the bone.
- Primarily to confirm liver or gallbladder as a source of elevated alkaline phosphatase rather than breakdown in the bone.
- GGT is also a sensitive marker for metabolic dysfunction.

LACTATE DEHYDROGENASE (LDH)

- Primarily a marker for tissue or cellular damage.

ALKALINE PHOSPHATASE

- Primarily a marker for liver and bone damage.
- When bone disease is excluded, an elevation of alkaline phosphatase suggests biliary obstruction, injury to the bile duct, epithelium, or cholestasis.
- Always retest to confirm high alkaline phosphatase.
- It is most likely marker of liver dysfunction when GGT is also high.
- If GGT is normal or equivocal, consider running alkaline phosphatase isoenzymes to see whether the elevation is coming from the intestine, the liver, or the bone.

LIVER DISEASE/ CAUSES OF ELEVATED LIVER ENZYMES

1. Chronic viral hepatitis

Form	Prevalence	Risk factors	Comments
Hepatitis C	1.8% of general population; rate much higher in people with known risk factors and ALT >40 IU/L	Blood transfusions (esp. before 1992), IV drug use, cocaine use, hemodialysis, organ transplantation, birth in endemic region	Many patients will have no symptoms or mild symptoms and only mildly elevated ALT/AST; if risk factors present, early testing warranted
Hepatitis B	0.2–0.9% of general population; as high as 20% after travel to endemic areas	Same as above; more commonly transmitted sexually than Hep C	Many patients will have no symptoms or mild symptoms and only mildly elevated ALT/AST; if risk factors present, early testing warranted

2. Iron overload
3. Alcoholic liver disease
    a. Risk: 10-plus years of more than 5 drinks, (12-ounce beer, 1.5 ounces of spirits, 5 ounce glass of wine)
    b. Often see AST-to-ALT ratio of 2 to 1
4. Nonalcoholic fatty liver disease
    a. Risk factors include patients with components of metabolic syndrome: abdominal obesity, insulin resistance, hyperlipidemia, hypertension, certain medications (corticosteroids, tetracycline, valproic acid, amiodarone)
5. Autoimmune hepatitis
    a. More common in women and those with other autoimmune diseases

   b. Diagnosis by exclusion of viral hepatitis, pathologic findings, and presence of autoimmune markers such as antinuclear antibodies, smooth muscle antibody, liverkidney microsomal antibodies

6. Wilson's disease
   a. Anyone under age 40 with abnormal liver enzymes should be evaluated, even in absence of neurologic or ocular findings; routine screening rarely helpful in patients over age 50.
   b. Genetic testing is of limited value because of large number of potential mutations of ATP7B gene;
   c. If a patient does have WD, screen family members
7. Alpha-1-antitrypsin deficiency
   a. A protease inhibitor made in the liver that protects both the liver and the lungs.
   b. Patients with emphysema or with a young sibling with liver failure are at higher risk.
   c. Common cause of liver disease in young children, but only a portion develop liver failure as adults
8. Drug- and toxin-related liver diseases
9. Extrahepatic causes
   a. Thyroid disorders. Screen for thyroid antibodies and run full thyroid panel
   b. Celiac disease. Test tissue transglutaminase levels
   c. Hemolysis. Test LDH and haptoglobin levels, reticulocyte count; infection is a possible cause
   d. Muscular disorders. Test creatine kinase and aldolase levels; screen for SLE (systemic lupus erythematosus

Hepatitis B, hepatitis C, iron overload, and nonalcoholic fatty liver disease are the most common causes of elevated AST and ALT. If you're able to exclude iron overload, hepatitis B, and hepatitis C, it is very likely that the patient has nonalcoholic fatty liver, especially if you can rule out Wilson's disease with copper, ceruloplasmin, and urine copper testing.

GALLSTONES

- The majority of people with gallstones will not develop symptoms.
- When symptoms do present, they can be either episodic or steady, and the pain is located in the upper abdomen. It can be severe and last for more than 30 minutes, and then there can be some accompanying features such as nocturnal onset, nausea, vomiting, and radiation through to the back.

GALLSTONE RISK FACTORS

Not modifiable	Modifiable
Family history	Obesity/metabolic syndrome/diabetes mellitus/dyslipidemia
Genetic predilection	Drugs - ceftriaxone, octreotide, thiazide diuretics, female sex hormones
Ethnic background	Reduced physical activity
Female sex	Rapid weight loss
Age	TPN
	Diet
	Underlying disease: cirrhosis, Crohn's disease

Cholecystitis usually occurs as a complication of gallstone disease. Chronic cholecystitis is chronic inflammatory cell infiltration of the gallbladder seen on histopathology. It is almost always associated with gallstones and is thought to be the result of recurring, acute cholecystitis attacks, which leads to fibrosis and thickening of the gallbladder.

Cholecystitis without gallstones is called acalculous cholecystitis or biliary dyskinesia. Acalculous cholecystitis has numerous risk factors, and the mechanism primarily involves gallbladder stasis and ischemia, resulting in local inflammatory responses in the gallbladder wall.

MARKERS OF IMPAIRED GALLBLADDER FUNCTION

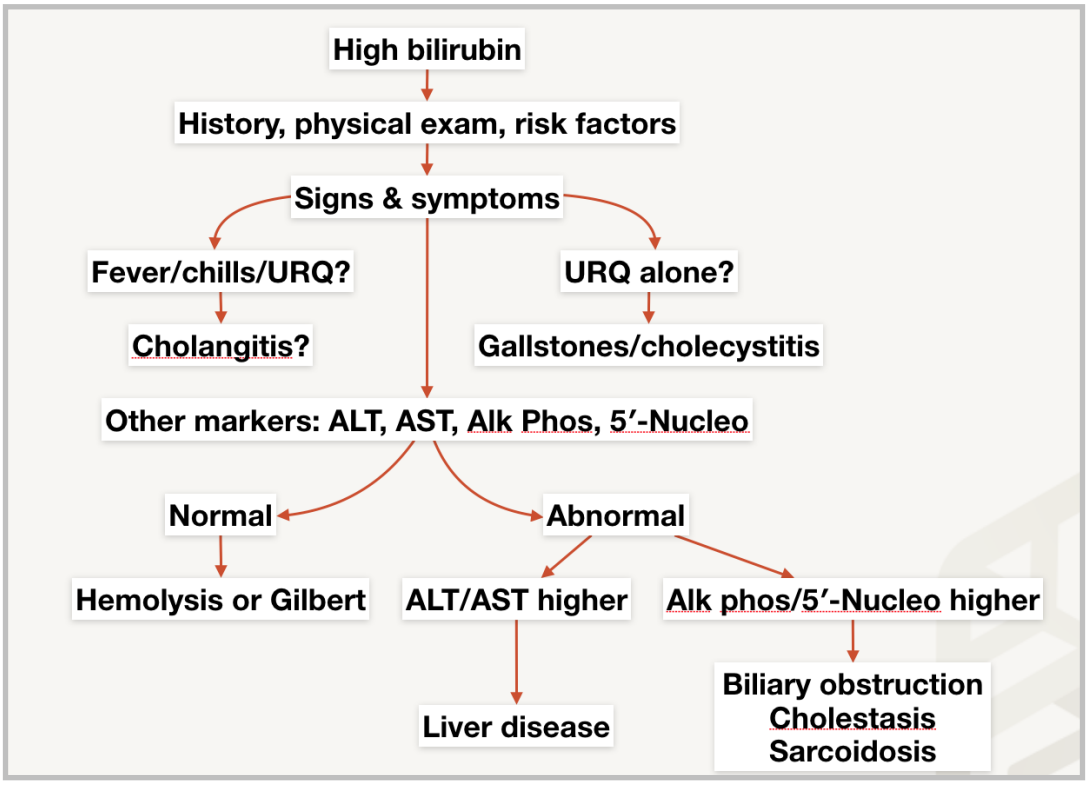
Similar to markers of liver dysfunction but with the addition of bilirubin and 5’-nucleotidase

Marker	Value
ALT	High
AST	High
Bilirubin	High
Alkaline phosphatase	High
5'-Nucleotidase	High
LDH	High
GGT	High

BILIRUBIN

- Normally, about 96 percent of bilirubin is unconjugated.
- Abnormalities of any of the four stages result in hyperbilirubinemia, with either high unconjugated bilirubin or both high unconjugated and conjugated bilirubin.
- In cases of high bilirubin, do a follow-up test for conjugated (direct) versus unconjugated (indirect).
- LabCorp can test total and direct bilirubin.
- Then you could subtract the direct (conjugated) bilirubin from the total bilirubin to get indirect (unconjugated).

ALGORITHM FOR HIGH BILIRUBIN



- High indirect or unconjugated bilirubin evaluation is based on whether the abnormalities are due to biliary obstruction, intrahepatic cholestasis, hepatocellular injury, or an inherited condition.
- If there is evidence of biliary obstruction such as high unconjugated bilirubin and high alkaline phosphatase and/or 5′-nucleotidase, then you can refer out for hepatic imaging such as ultrasound or MRI.
- If there is evidence of liver disease, such as higher AST and ALT than alkaline phosphatase or 5′-nucleotidase, do further testing for causes of liver issues such as Wilson disease, hemochromatosis, hepatitis, etc.

ALKALINE PHOSPHATASE

Note that when the values of alkaline phosphatase are markedly elevated, such as more than four times the upper end of the range, it is more likely to be due to obstructive pathology such as bile duct stones, an infection, or cirrhosis. Intestinal alkaline phosphatase could increase in states of dysbiosis or disrupted gut microbiome as a means of detoxifying LPS lipopolysaccharide.

5′-NUCLEOTIDASE

The primary purpose of 5′-nucleotidase clinically is to confirm that high alkaline phosphatase is a marker of liver or gallbladder dysfunction and not bone or intestinal issues.

LACTATE DEHYDROGENASE (LDH)

- LDH is elevated in gallbladder cancer, cholelithiasis, and chronic cholecystitis.
- If LDH is elevated, look at bilirubin and alkaline phosphatase.
    - If those two are elevated, run LDH isoenzymes.
    - If LDH isoenzymes 3 and 4 are significantly elevated, refer for gallbladder cancer screen.
- If there is another pattern, address the underlying causes and retest.
- If bilirubin and alkaline phosphatase are not elevated, you should still run LDH isoenzymes to see where the elevation is coming from.

INDICATIONS FOR HIGH GGT

- Confirm liver/gallbladder origin of high alkaline phosphatase
- Alcohol abuse or alcoholic liver disease
- Metabolic dysfunction
- Cardiovascular disease
- Iron overload

TREATMENT/PREVENTION OF GALLBLADDER DYSFUNCTION

- Weight loss
- Increase physical activity
- Paleo *(gluten-free)* diet
- Discontinue drugs that harm gallbladder
- Address underlying conditions

SUPPLEMENTS AND BOTANICALS FOR GALLBLADDER DYSFUNCTION

Intervention	Comments
Bitters	Help with bile synthesis and metabolism
Other botanicals	Help with bile synthesis and metabolism
Phosphatidylcholine	Prevents and possibly dissolves gallstones
Vitamin C	Prevents gallstones
Rowachol	May dissolve gallstones
Ox bile / bile salts	Acts as “bile replacement”