Evaluation of Abnormal Liver Chemistries for Primary Care Providers

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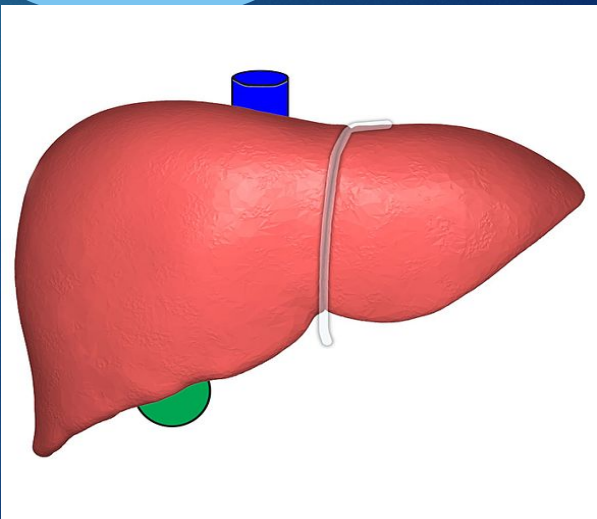


Background

- Approximately 8% of the US population has elevated liver enzymes
- Medical history and serologic evaluation leads to a diagnosis in most cases
- Of those patients with a negative serologic evaluation, 77% are due to alcoholic or non-alcoholic fatty liver disease
- Alcoholic liver disease diagnosed by history
- NAFLD diagnosed by imaging (detection dependent on sensitivity of the imaging study used)

Tapper EB NEJM 2017:377;756-68

Evaluation of Abnormal Liver Chemistries

- **Aspartate aminotransferase** (AST): present in liver, cardiac muscle, skeletal muscle, kidney, and brain.
- **Alanine aminotransferase** (ALT): primarily liver but can be seen in with skeletal muscle injury.
- **Alkaline phosphatase**: Found in hepatocytes on the canalicular membrane, bone, placenta, intestine, and kidney. Can be elevated after a fatty meal due to intestinal source.
- **Bilirubin**: From the breakdown of old red blood cells with the majority circulating bound to albumin in the unconjugated form. *Unconjugated* bilirubin is hydrophobic and not excreted in urine. *Conjugated* bilirubin is hydrophilic and excreted in the bile and converted to urobilinogen by gut bacteria and excreted in urine and stool.

ACG guidelines 2017

Evaluation of Abnormal Liver Chemistries

- When to fractionate the total bilirubin?
  - When ALT, AST, and alkaline phosphatase are normal or near normal.
  - Unconjugated hyperbilirubinemia- hepatocellular disease is unlikely.
  - Conjugated hyperbilirubinemia- hepatocellular disease, cholestatic liver disease.

Evaluation of Abnormal Liver Chemistries

- Markers of hepatocellular function are albumin and prothrombin time, total bilirubin
- Albumin synthesized solely by the liver with a half-life of 3 weeks. If ≤ 3.5 g/dl indicative of liver disease or severe systemic disease due to cytokine effects.
- PT is more sensitive as can reflect liver dysfunction within 24 hours of the event. Measures activity of factors 1, 2, 5, 7, 9 and 10. Note: Vit K dependent factors are 2, 7, 9, 10.

Evaluation of Abnormal Liver Chemistries: Summary

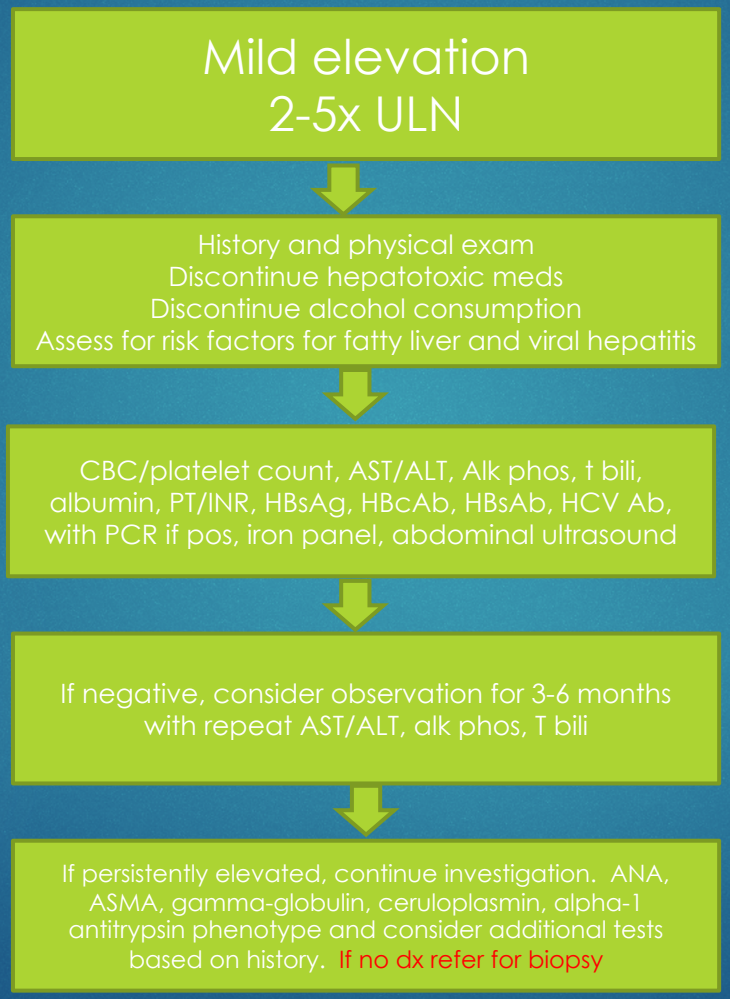
- Liver Chemistries: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin
- Markers of hepatocellular function: albumin, bilirubin, prothrombin time
- Hepatocellular injury: AST, ALT, alkaline phosphatase elevation
- ALT more specific marker of liver injury than AST
- Confirmation that alkaline phosphatase is of liver origin by checking GGT or fractionation of alkaline phosphatase

What is a normal liver chemistry?

- Normal lab values defined as the mean value of the healthy population ± 2 standard deviations
- Normal ALT and AST values has been problematic due to differences in defining healthy populations.
- Elevated ALT or AST above the ULN in a population without identifiable risk factors is associated with increased liver related mortality
- Linear relationship between ALT level and BMI
- Normal ALT does not exclude liver disease
- ALT higher in males than females
- Normal values for ALT and AST vary from lab to lab

Approach to Patients with Elevated AST and ALT

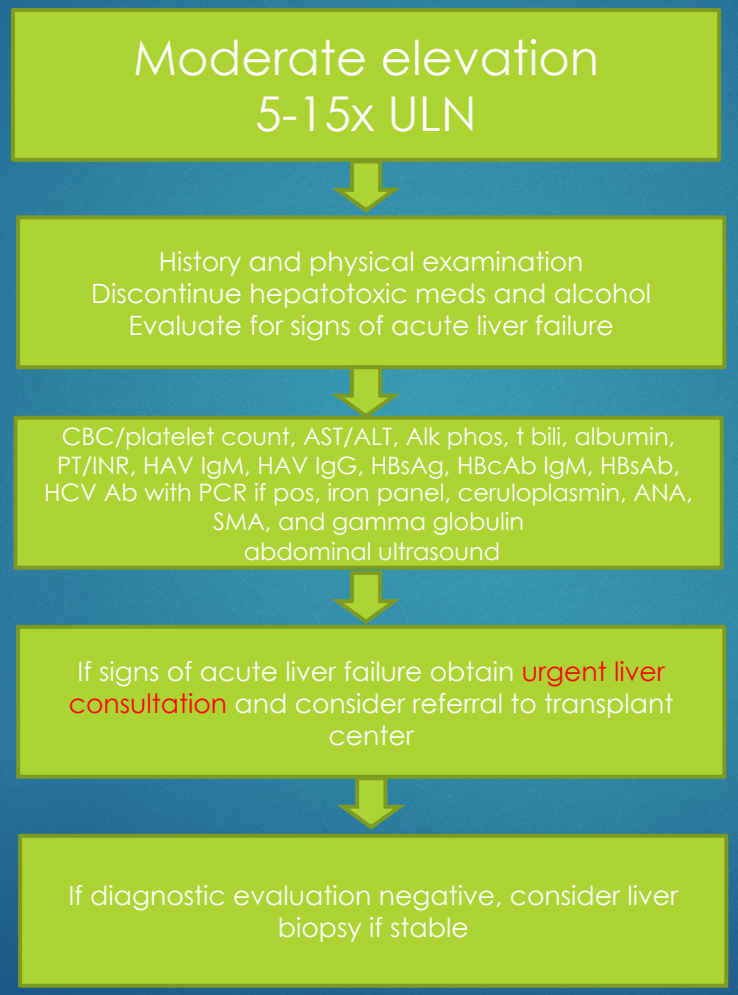
Approach to Patients with Elevated AST and ALT



Diagnoses to Consider with Borderline to Mild Elevations of Liver Chemistries

- NAFLD esp in patients with metabolic syndrome
- Chronic hepatitis C in patients with a history of intranasal or intravenous drug use, tattoos, body piercings, blood transfusions, high risk sexual activity, baby boomers (born 1945-1965)
- Chronic hepatitis B in patients from areas of high endemicity, men who have sex with men, iv drug users, dialysis patients, HIV-infected, pregnancy women, contacts.
- Alcoholic liver disease in women who consume more than 140 g/week, men consuming more than 210 g/week
- Hemochromatosis, autoimmune hepatitis, alpha-1 antitrypsin deficiency, Wilson's disease, PBC
- Drugs and supplements

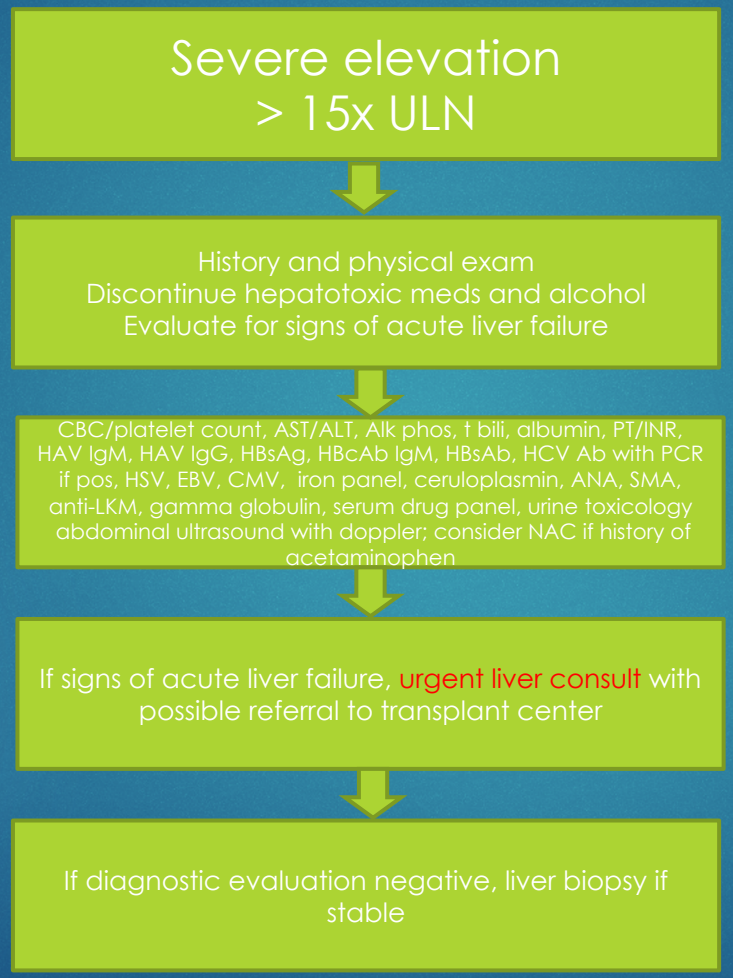
Approach to Patients with Abnormal Liver Chemistries



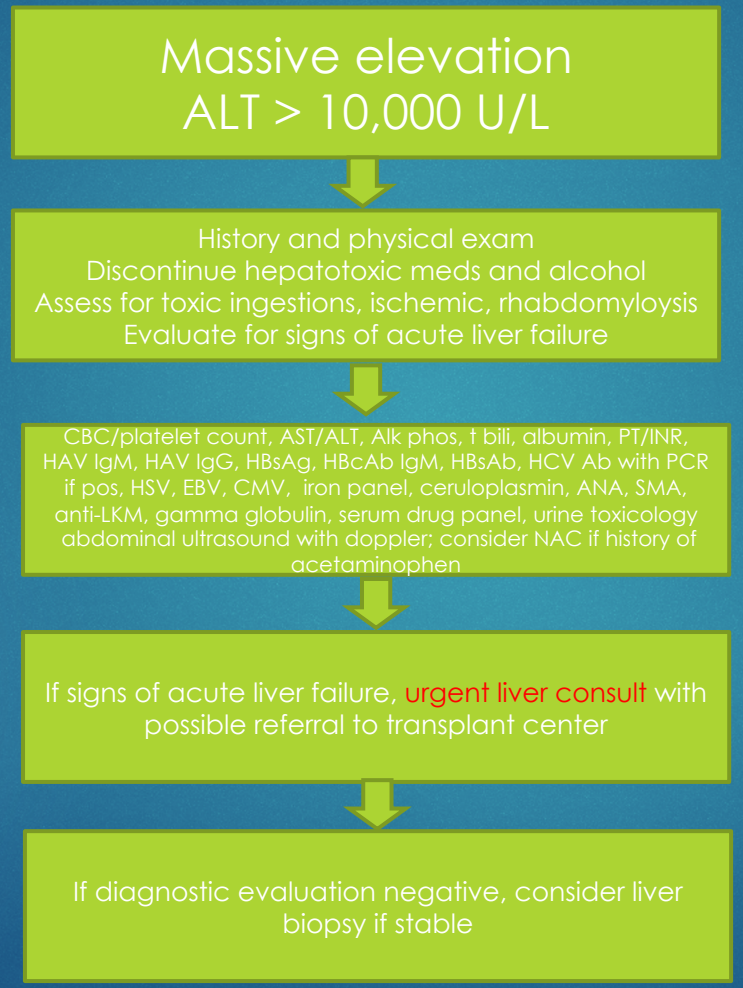
Diagnoses to Consider with Moderate Elevations in Liver Chemistries

- Acute viral hepatitis A, B or C
- Drugs or supplements
- Autoimmune hepatitis
- Wilson's disease

Approach to Patients with Elevated AST and ALT



Approach to Patients with Abnormal Liver Chemistries



Diagnoses to Consider with Severe or Massive Elevation in Liver Chemistries

- Acetaminophen toxicity
- Ischemic Hepatopathy
- Drugs and supplements

Causes of elevated AST and ALT

- **Hepatic** (generally AST > ALT):
  - alcoholic liver disease
  - cirrhosis
  - ischemic hepatitis
  - congestive hepatopathy
  - acute Budd-Chiari syndrome
  - hepatic artery damage/thrombosis/occlusion
  - TPN

Causes of elevated AST and ALT

- **Hepatic** (generally ALT> AST):
  - NAFLD present in ~ 30% US population
  - chronic and acute viral hepatitis: chronic hepatitis C 3 million, chronic hep B 1.5 million
  - DILI (livertox.nih.gov): antibiotics, anti-epileptics, acetaminophen, NSAIDS, statins, anti-TB, HIV drugs, biologics, green tea extract, shark cartilage, chaparral, ephedra, ji bu huan
  - toxic hepatitis (amanita exposure)
  - hemochromatosis: homozygous C282Y 1 in 220-250 Northern European Caucasians
  - autoimmune hepatitis
  - Wilson's disease: autosomal recessive 1:30,000
  - alpha-1 antitrypsin deficiency: more common in children 1:2500 in North American Caucasians

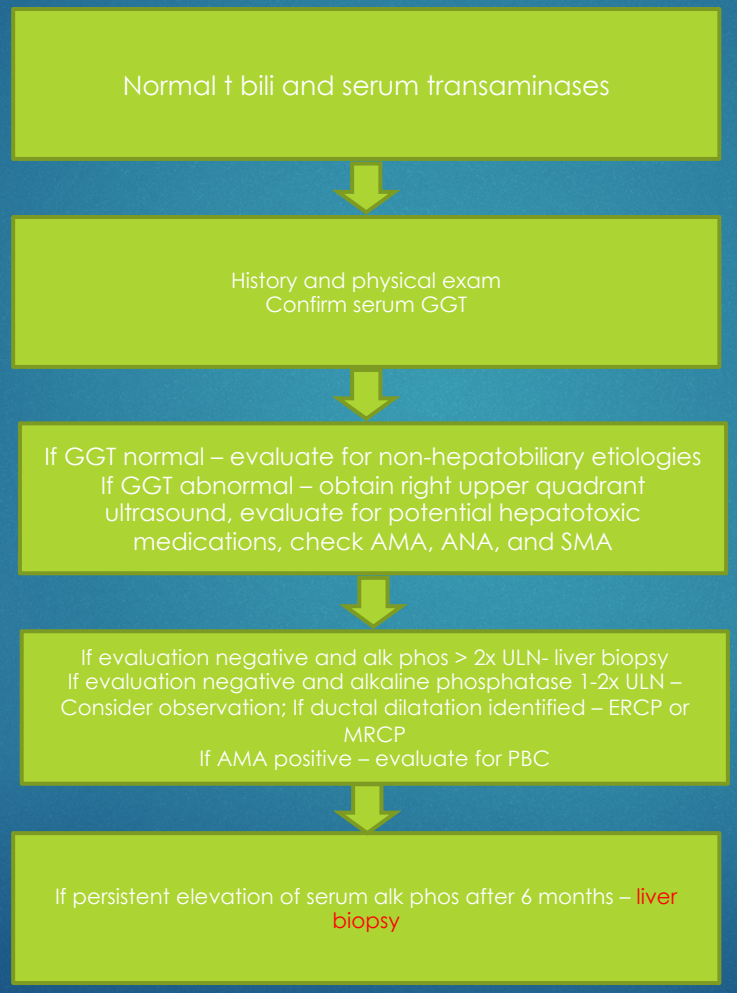
Causes of elevated AST and ALT

- **Hepatic** (generally ALT> AST):
  - Celiac disease
  - acute bile duct obstruction
  - liver trauma, post liver surgery
  - sinusoidal obstruction syndrome
  - diffuse infiltration of liver with cancer
  - HELLP, acute fatty liver of pregnancy
  - Sepsis
  - hemophagocytic lymphohistiocytosis.

Causes of elevated AST and ALT

- **Non-hepatic**:
  - skeletal muscle damage
  - cardiac muscle damage
  - thyroid disease
  - Macro-AST
  - strenuous exercise
  - heat stroke
  - hemolysis
  - adrenal insufficiency

Approach to Patients with Elevated Alkaline Phosphatase



Approach to Patients with Elevated Alkaline Phosphatase

Causes of elevated alkaline phosphatase

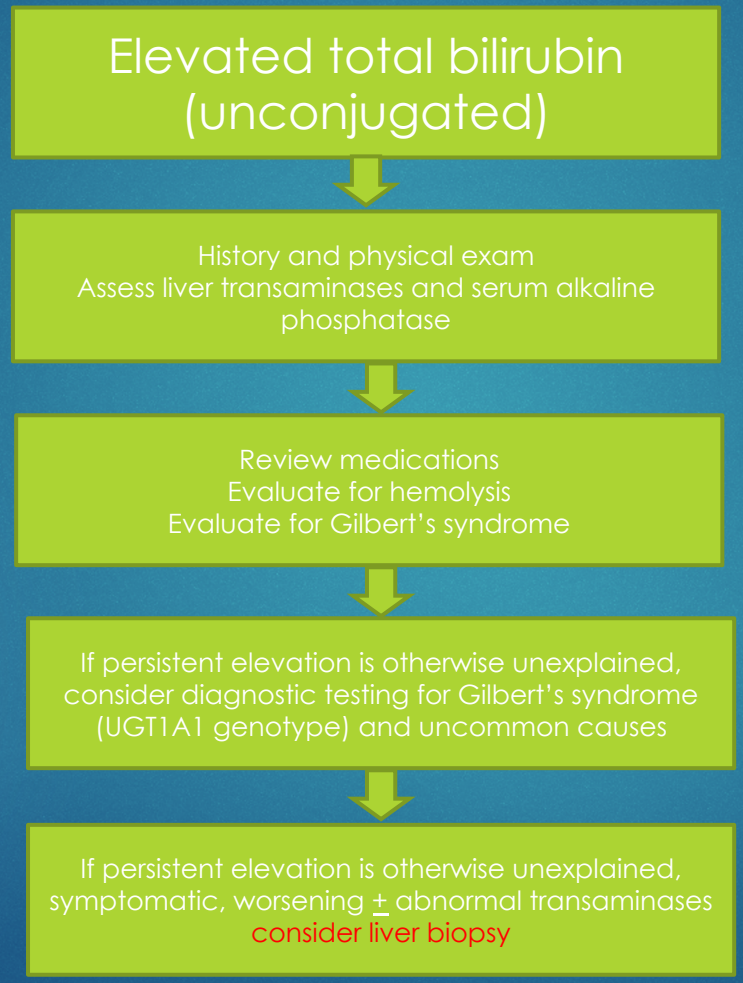
- **Cholestatic liver diseases**
  - Primary biliary cholangitis (PBC)
  - Primary sclerosing cholangitis (PSC) esp in the setting of inflammatory bowel disease, elevated IgG4
- **Hepatobiliary disease**: biliary obstruction
- **DILI**
- Infiltrative disease of the liver
- Hepatic abscess
- Malignancy
- Cirrhosis
- Rare causes: vanishing bile duct syndrome, ICP, TPN, and others

Causes of elevated alkaline phosphatase

- Non-hepatic
  - Bone disease
  - Hyperparathyroidism
  - Pregnancy (third trimester)
  - Chronic renal failure
  - Lymphoma
  - Extra-hepatic malignancy
  - Congestive heart failure
  - Childhood growth
  - Infection
  - Inflammation

- Non-hepatic
  - Fatty meal
  - Gastric ulcer
  - Blood type O and B
  - Myeloid metaplasia
  - Peritonitis
  - Diabetes Mellitus
  - Increasing age, esp women

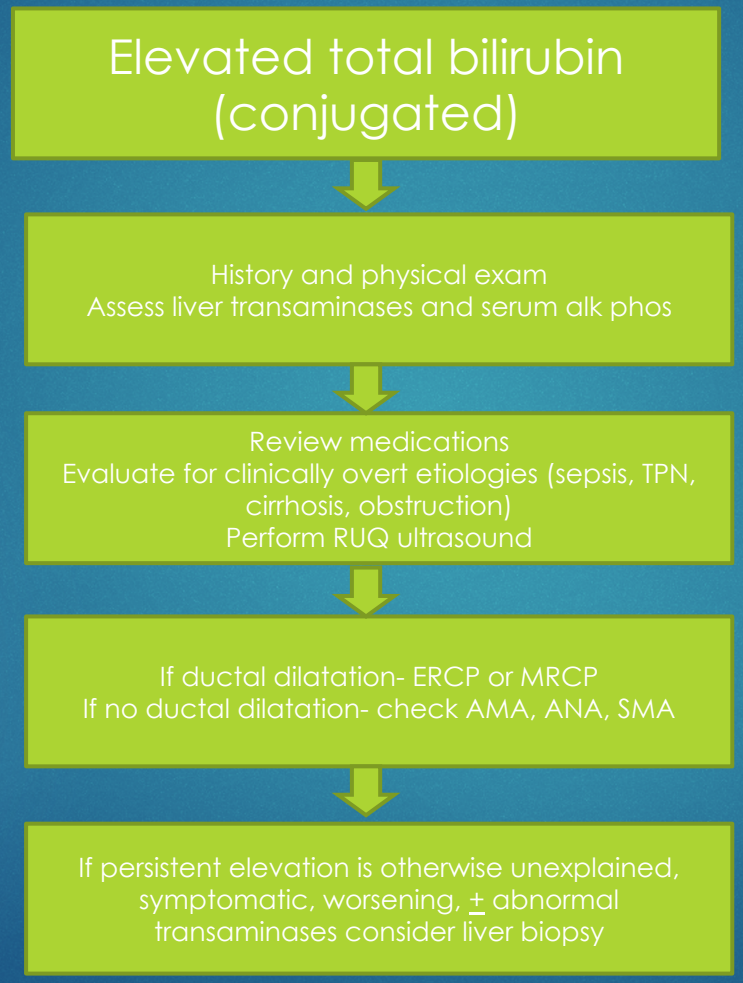
Approach to Patient with Elevated Total Bilirubin



Causes of Elevated Unconjugated Bilirubin

- **Gilbert's syndrome**
- Crigler-Najjar syndrome
- **Hemolysis (intravascular and extravascular)**
- Ineffective erythropoiesis
- Neonatal jaundice
- Hyperthyroidism
- Medications
- Post-blood transfusion

Approach to Patients with Elevated Total Bilirubin



Causes of Elevated Conjugated Bilirubin

- **Bile duct obstruction**
- AIDS cholangiopathy
- **Viral hepatitis**
- Toxic hepatitis
- **Medications or drug-induced liver injury**
- **Acute alcoholic hepatitis**
- Ischemic hepatitis
- **Cirrhosis**
- **Primary biliary cholangitis**
- PSC
- Infiltrative liver diseases
- Wilson's disease
- **Autoimmune hepatitis**
- Congestive Hepatopathy
- Sepsis
- TPN
- Intrahepatic cholestasis of pregnancy
- Benign post-operative jaundice
- ICU jaundice
- Benign recurrent cholestasis
- Vanishing bile duct syndrome
- Ductopenia
- Dubin-Johnson syndrome
- Rotor Syndrome
- Sickle Cell liver crisis
- Hemophagocytic lymphohistiocytosis

Evaluation of Abnormal Liver Chemistries: Summary

- When to refer?
  - Screen for viral hepatitis
    - Hepatitis A: anti HAV total for routine health maintenance to assess need for vaccination; anti HAV IgM to assess for acute hepatitis A
    - Hepatitis C: anti-HCV, if positive HCV RNA quant and genotype
    - Hepatitis B: If concerned about acute hepatitis B check Hep BsAg, anti HBc IgM, Hep BsAb (health maintenance); if Hep BsAg+ check HBV DNA
  - Screen for iron overload: check TSI, TIBC, ferritin
  - Screen for hepatic steatosis: abdominal ultrasound
  - If positive tests, refer for further evaluation except when testing for immunity.