

Abnormal LFTs - Common Etiologies & Diagnoses NOT to Miss!

David J. Hass, MD FACP

Associate Clinical Professor of Medicine

Yale University School of Medicine

PACT Gastroenterology Center, A Division of HHC

Patterns of Liver Test Elevation

- Hepatocellular Elevation (AST/ALT)
- Cholestatic (Alkaline Phosphatase/Bilirubin)
- Infiltrative (Predominantly Alkaline Phosphatase)
- Mixed
- Transaminases >1000

Elevated AST/ALT Differential Diagnosis

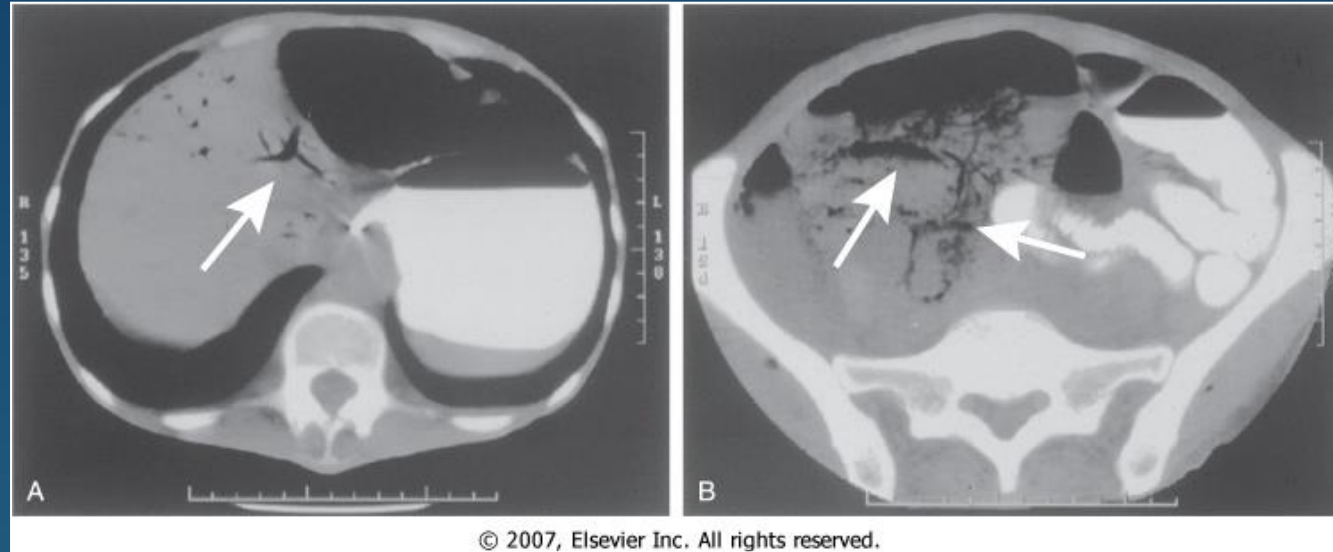
- Vascular
- Metabolic
- Infectious
- Medications

Differential diagnosis of mildly and moderately elevated serum aminotransferases (<15 times upper limit of normal)

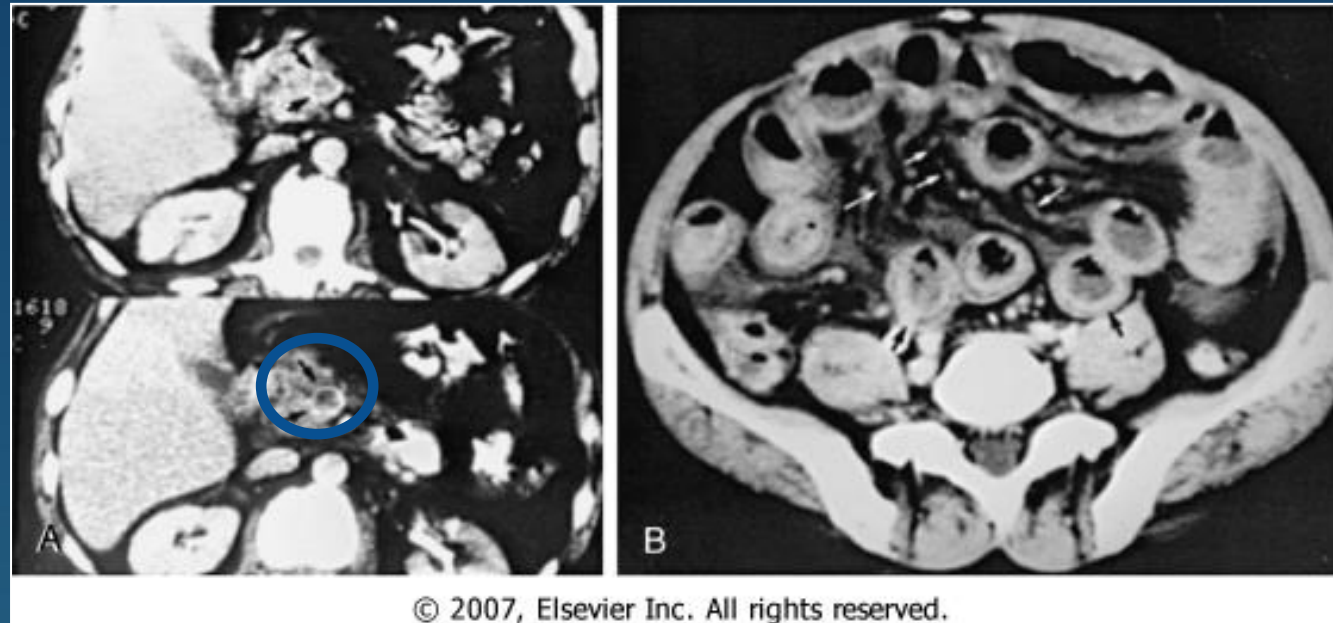
Hepatic disease		Nonhepatic disease
ALT predominant (AST/ALT <1)	AST predominant (AST/ALT ≥1)	
Drug-induced liver injury	Alcohol-associated hepatitis	Muscle injury (strenuous exercise, myopathy)
Chronic viral hepatitis (HBV, HCV)	Cirrhosis due to viral hepatitis or NAFLD	Adrenal insufficiency
Occupational, toxin-related hepatocellular damage	Wilson disease	Myocardial infarction, heart failure
Autoimmune hepatitis		Anorexia nervosa
NAFLD		Thyroid disease
Genetic disorders <ul style="list-style-type: none"> ▪ Wilson disease ▪ Hemochromatosis ▪ Alpha-1 antitrypsin deficiency 		Celiac disease
Congestive hepatopathy		Macro-AST
Malignant infiltration of the liver		

A Case...

- 26 year-old woman
- 4 days of intermittent abdominal pain
- Mild distention, otherwise normal physical exam
- Multiple miscarriages in later stages of pregnancy
- WBC 18, HCO₃ 20 AST/ALT 400/560 Normal bilirubin and alk phos



ACUTE MESENTERIC ISCHEMIA



MESENTERIC VENOUS THROMBOSIS

Acute Mesenteric Ischemia

- Arterial:
 - Embolism – SMA Embolus
 - Thrombosis – SMA Thrombosis
 - Non-occlusive mesenteric ischemia – NOMI
 - Focal segmental ischemia
- Venous:
 - **Mesenteric Venous Thrombosis**

Acute mesenteric ischemia

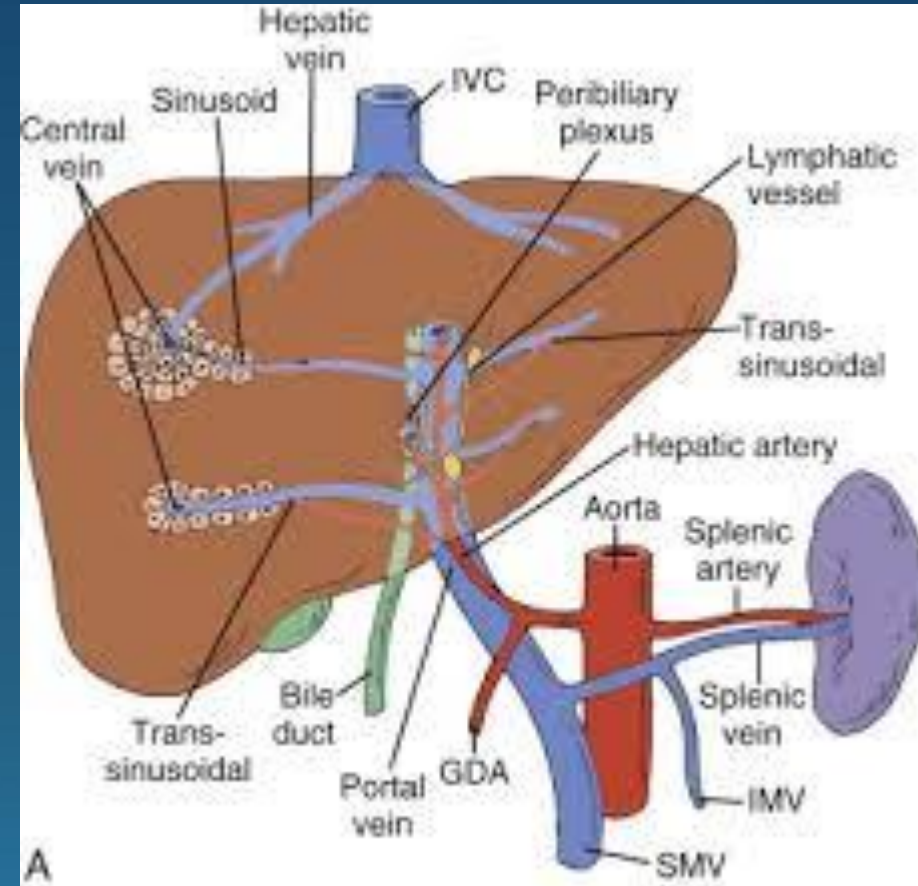
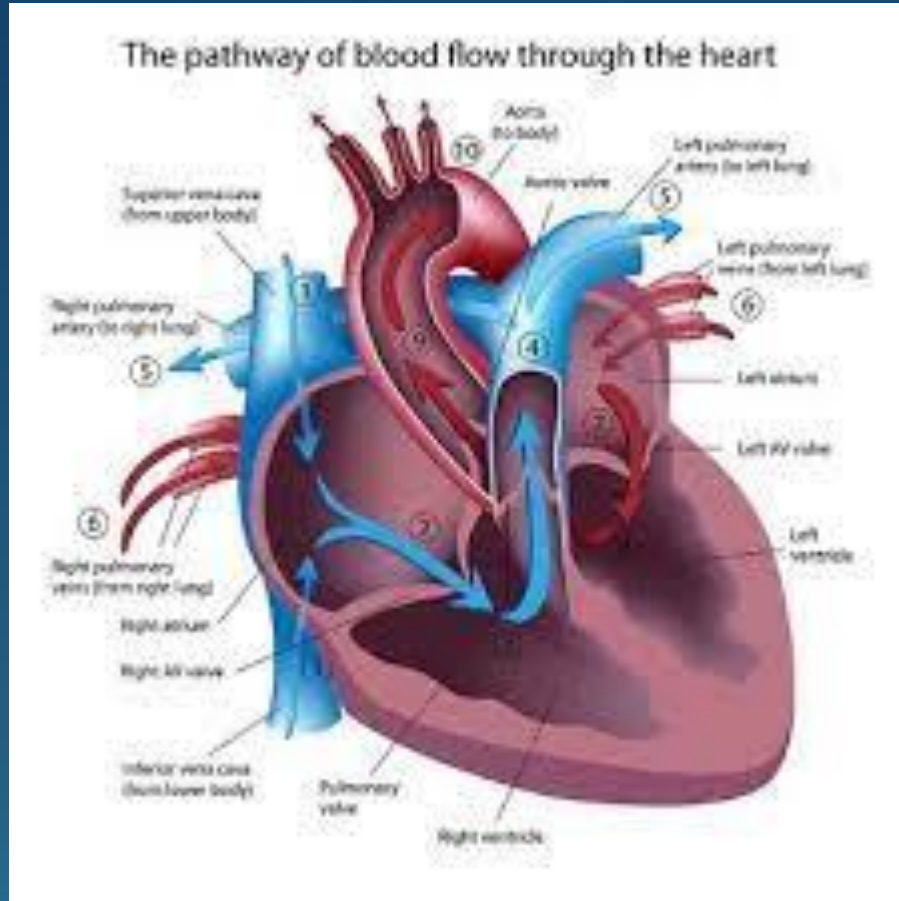
CAUSE	FREQUENCY
SMA Embolus	50%
NOMI	25%
SMA Thrombosis	10%
Mesenteric Venous Thrombosis	10%
Focal Segmental Ischemia	5%

Mesenteric Venous Thrombosis

- Hypercoagulable states
- Estrogen therapy
- PCV
- Neoplastic disease
- Pregnancy
- Portal Hypertension
- Inflammation
- Post-operative State

- Remember to keep ischemia in differential diagnosis for abdominal pain and elevated LFTs

Other vascular causes of increased AST/ALT



Vascular Causes of Increased LFTs

- Pericarditis
- Pulmonary Embolism
- Pulmonary Hypertension/Pulmonic Stenosis
- Tricuspid Valve Stenosis
- IVC thrombosis
- HV thrombosis
- Sinusoidal disease
- Portal Vein thrombosis/Mesenteric Venous Thrombosis

Clinical Exam

- THINK OF MESENTERIC ISCHEMIA EARLY!!!!
- PAIN OUT OF PROPORTION TO EXAM!!!!
- Acute vs. Subacute

- Abdominal pain, tenderness, distention
- Absent bowel sounds
- Hypotension
- GI bleeding (rectal bleeding, melena)
- Mental status change

Another Case...

- 44 year-old male
- Referred for mild elevation of liver tests and arthropathy
- PE: Appears tan, 2nd and 3rd digits with swelling and pain
- AST/ALT 200/310 Normal bilirubin and alk phos
- Ferritin 1200, Iron saturation 78%

Diagnosis?

Hemochromatosis Diagnosis

- Autosomal recessive
- HFE gene (C282y or H63D mutations)
- Ferritin >1000 and iron saturation >50%
- Age presentation in women later than men

Hemochromatosis Presentation

- Hepatic involvement
- Cardiac (cardiomyopathy, heart failure, arrhythmia)
- Hypogonadism
- Skin Pigmentation
- Joint involvement with arthropathy

Hand arthritis in hemochromatosis



Serial radiographs, five years apart, of the metacarpophalangeal joints in a patient with hereditary hemochromatosis (HH). The second image shows loss of joint space at the second and third metacarpophalangeal articulations, cyst formation, and a hook-like osteophyte on the radial aspect of the metacarpal head of the third finger (arrow).

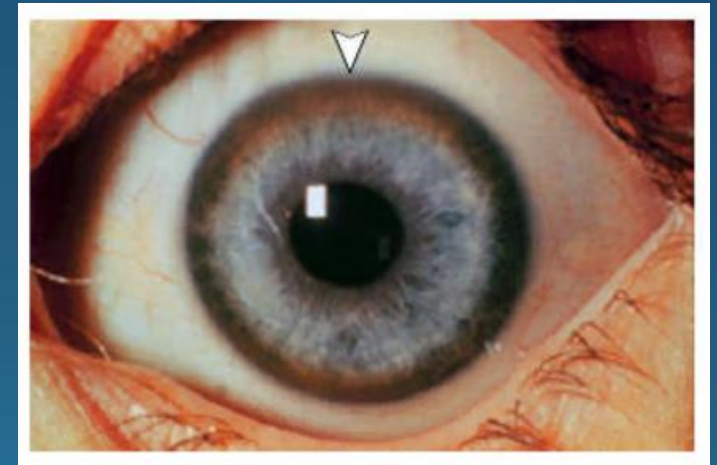


Hemochromatosis Treatment

- MRI for iron quantification of both liver and heart
- Therapeutic phlebotomy
 - 500cc q week until Ferritin <50 and Hb <12
- Screening for HCC if cirrhosis
- Screening of 1st degree relatives

Another case...

- 25 year-old male
- Referred for mild elevation of liver tests and chorea of his arms/mental status changes and micrographia
- PE: Hemiballismus/Mental status changes
- AST/ALT 200/310; **LOW** alkaline phosphatase



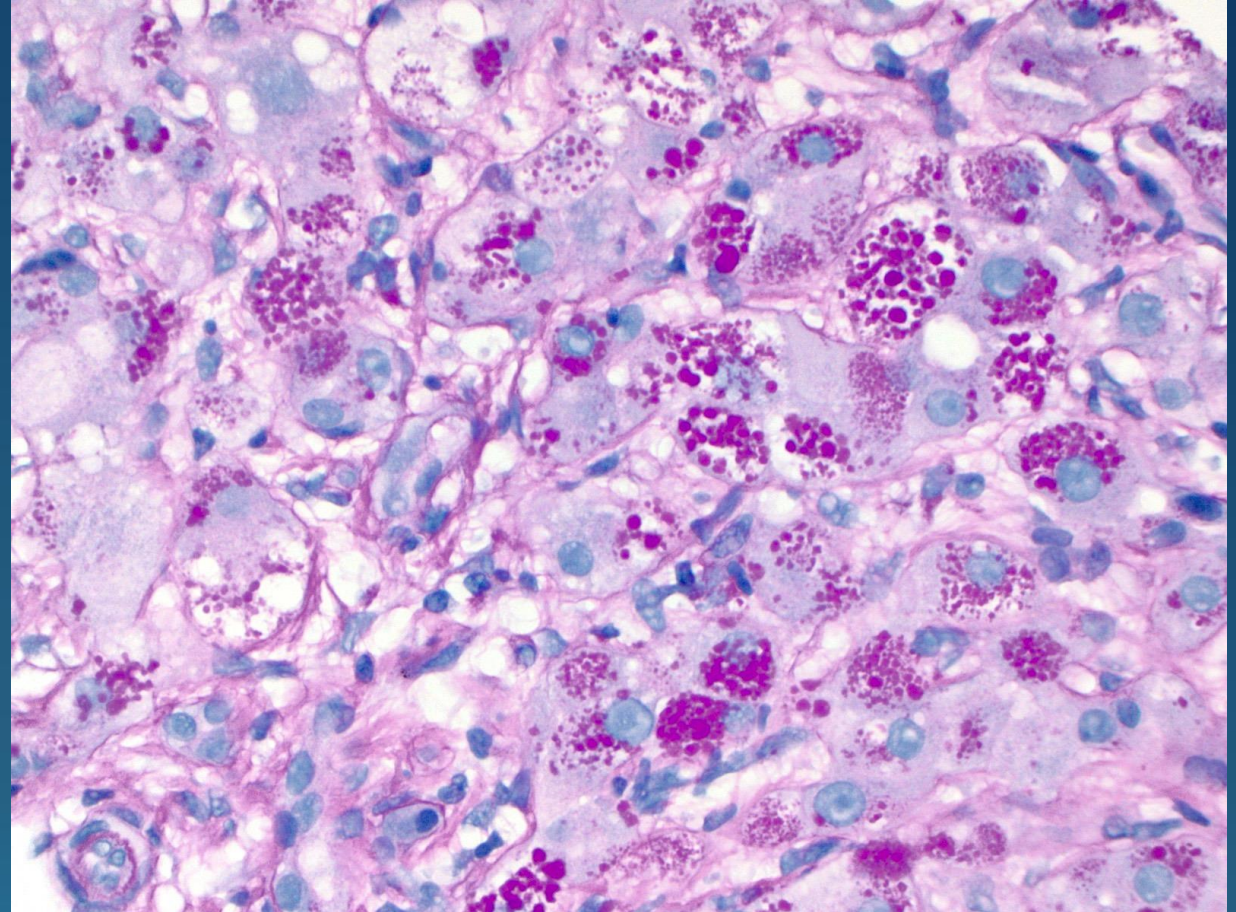
Wilson's Disease

- Autosomal recessive
- Impaired function of intracellular copper transporter ATP7B
- Low ceruloplasmin/Increased urinary copper excretion/hepatic copper quantification ($>250\text{mg/g}$)
- Keyser-Fleischer Rings/Sunflower cataracts
- Excessive copper accumulation in liver, brain and cornea
- Tx: metal chelating agent (trientene/penicillamine)/Liver transplant

Another Case...

- 39 year-old female
- Referred for mild elevation of liver tests and SOB/dyspnea
- PE: Pursed lip breathing. Barrel chested. Clubbing on exam.
- AST/ALT 240/310 Normal bilirubin and alk phos

Diagnosis?

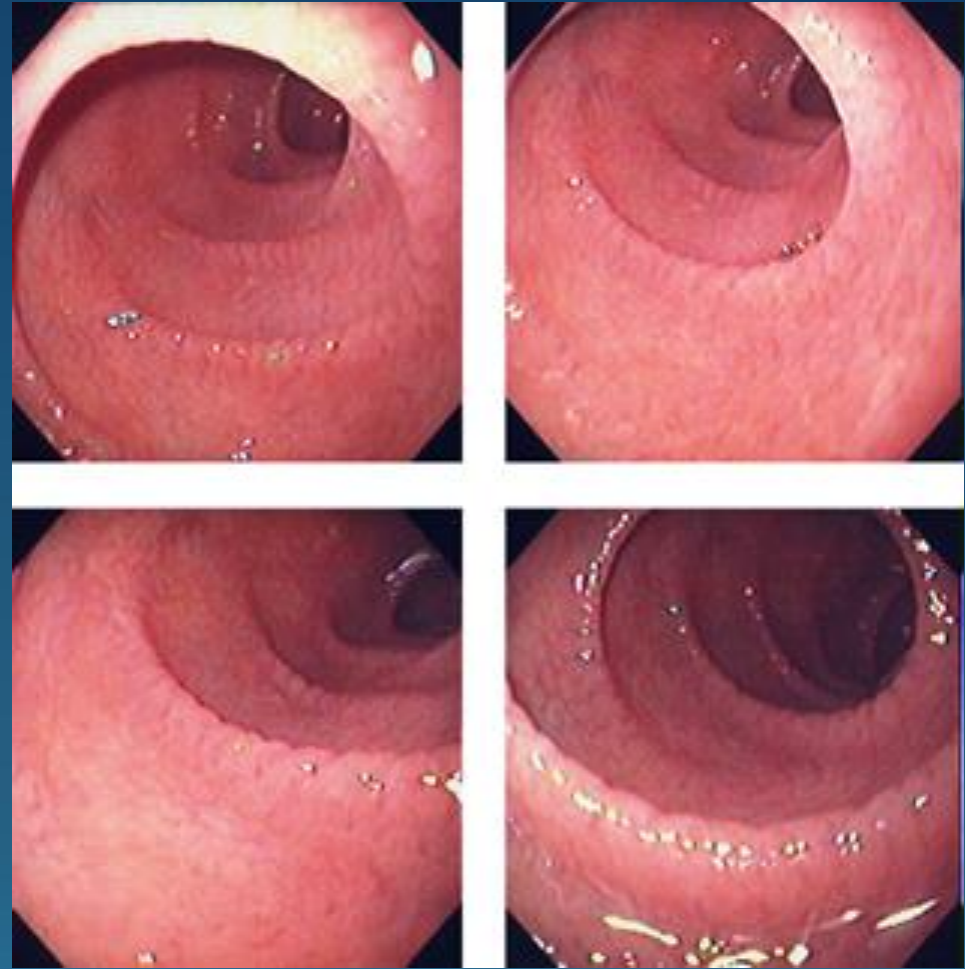


Alpha 1 Anti-trypsin deficiency

- Autosomal co-dominant transmission
- Liver pathophysiology vs. lung pathophysiology (bibasilar predominant, PTX)
- Z allele is abnormal. PiZZ usually results in clinical disease
- Under recognized – estimates of 3 million people worldwide
- Diagnosis: Serum AAT level (<20) and genetic testing of SERPINA₁ gene
- Treatment: Weekly AAT infusions

Other Metabolic Causes of Increased LFTs

- Metabolic dysfunction-associated steatohepatitis (MASH)
- Autoimmune Hepatitis (think elevated immunoglobulins)
- Celiac disease (Iron deficiency, anemia, osteoporosis, GI symptoms, rash)
- Adrenal Insufficiency (Markedly tan, vague abdominal pain)
- Thyroid Disease



Another Case...

- 40 year-old female born in Argentina referred after family planning labs
- Referred for mild elevation of liver tests, abnormal HBV serologies and rash
- PE: Hepatomegaly. Erythematous painful nodules on lower extremities
- AST/ALT 240/300 HBsAg + HBcAb +

Next steps?



Hepatitis B

- Further labs:
 - HBsAb negative, HBsAg positive, HBcAb positive
 - HBV DNA level 100,000 copies/mL
 - HBeAg - HBeAb +
 - HCV Ab negative
 - HAV IgM/IgG negative
 - ANCA positive

Next steps?

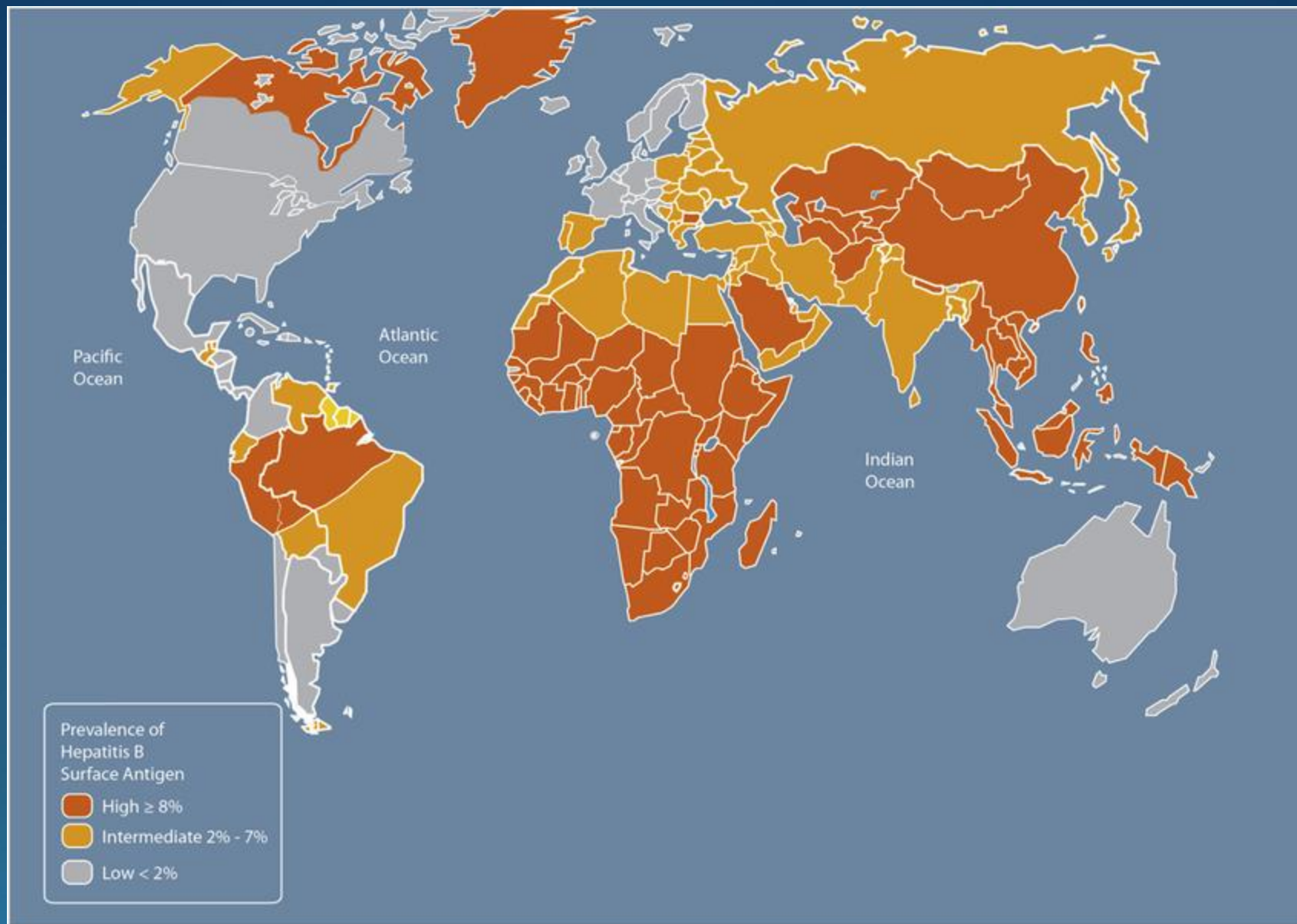
Hepatitis B

	Acute infection	Resolved infection	Chronic infection	History of vaccination
<i>HBs Ag</i> Recent infection	Detected	Not detected	Detected	Not detected
<i>HBs Ab</i> Produced to fight HBV	Not detected	Detected	Not detected	Detected
<i>HBc Ab</i> History of infection	Detected	Detected	Detected	Not detected

Note. HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus. Information from Hepatitis B Foundation (2012).

Hepatitis B

- Needs US and AFP (DNA virus)
- Vaccination for HAV
- Initiate therapy with anti-viral (Tenofovir)
- Baby will need HBIG and Immediate vaccination on delivery
- Vaccinate all household contacts



Infectious Causes of Elevated Transaminases

- Viral
 - HAV, HBV, HCV, HDV, HEV, HGV, CMV, EBV, HIV, VZV, HSV, Adeno, COVID
- Bacterial
 - Leptospirosis (Temperature/pulse dissociation)
 - Bartonella
 - Fitz-High Curtis Syndrome
- Mycobacterium
- Parasitic (Amebiasis, Schistosomiasis, Ecchinococcus)
- Rickettsial Disease (Lyme, RMSF, Babesiosis)

Drug Induced Liver Injury

- DILIRank: the largest reference drug list ranked by the risk for developing drug-induced liver injury in humans.

Chen M., Suzuki A., Thakkar S., Yu K., Hu C., and Tong W.

Drug Discov Today. 2016, 21(4): 648-653.

Drug Induced Liver Injury

- Statins
- Acetaminophen
- Azathioprine
- Estradiol
- Methotrexate
- Phenytoin
- Allopurinol
- Amiodarone
- Isoniazid
- TMP/SMX –cholestasis
- Diclofenac (AIH histology)
- Ketoconazole
- SSRIs
- Rosiglitazone
- Fluconazole
- Nitrofurantoin
- Amoxicillin Clavulanic Acid
- Erythromycin
- **CBD oil**
- Aloe, Black cohosh, Ephedra, Kava
- **MDMA** (Bruxism/Hyperthermia)

Transaminases >1000

- Acetaminophen toxicity
- Acute viral hepatitis
 - Hepatitis A, B, C, D, E; herpes simplex virus; varicella zoster virus; Epstein-Barr virus; cytomegalovirus, other viral infections; or an acute exacerbation of chronic viral hepatitis (hepatitis B)
- Ischemic hepatitis
- HELLP Syndrome
- Acute fatty liver of pregnancy
- Autoimmune hepatitis
- Wilson disease
- Mushroom poisoning (*Amanita phalloides*)



Summary

- Liver test abnormalities can have different patterns
- Keep a broad differential when analyzing including CAM therapies
- Consider the following categories:
 - Vascular
 - Metabolic
 - Infectious
 - Medication Induced



Thank you for your attention. Questions?

dhass@gastrocenter.org