Abnormal Liver Chemistries in the “Asymptomatic” Patient

Linda Davis, MD
Medical Director and Founder
Kolvita Family Medical Group
Mission Viejo, CA

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Learning Objectives

- Explain the initial work-up for abnormal liver chemistries in the “asymptomatic” patient
- Identify causes for abnormal liver chemistries
- Discuss the diagnosis and management of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

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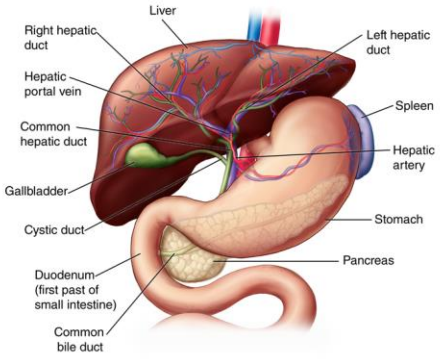
The Liver

- Large organ in right upper quadrant of abdomen
- Normal weight in adults = 1200-1500g
- Processes 20% of body’s blood volume/min
  - 75% via portal vein
  - 25% via hepatic artery
- For some, the liver (not human hopefully) is considered a delicacy and goes well with onions



Francque S., Marchesini G., Kautz A., et al. Non-alcoholic fatty liver disease: A patient guideline. © 2021 The Authors. Published by Elsevier B.V. on behalf of European Association for the Study of the Liver (EASL). Open access article under the CC BY-NC-ND license (http://creativecommons.org/ licenses/by-nc-nd/4.0/). https://easl.eu/wp-content/uploads/2021/09/Non-alcoholic-fatty-liver-disease-A-patient-guideline-final.pdf

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More than “Liver and Onions”

- Chemical factory of the body
- Receives blood from the gut via portal vein carrying nutrients (and any toxins absorbed) after a meal
- First point where nutrients are filtered and processed
- Metabolizes ingested drugs into nontoxic substances that can be utilized by the body

https://www.hopkinsmedicine.org/health/conditions-and-diseases/liver-anatomy-and-functions

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Primary Functions of the Liver

- Bile production and excretion
- Enzyme activation
- Metabolism of fats, proteins, and carbohydrates
- Excretion of bilirubin, cholesterol, hormones, and drugs
- Storage of glycogen and minerals
- Synthesis of plasma proteins such as clotting factors and albumin

https://www.hopkinsmedicine.org/health/conditions-and-diseases/liver-anatomy-and-functions

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The Most Common “Players” (Liver Chemistries)

- ALT (serum alanine aminotransferase) aka SGPT
  - Normal range: 7-56 U/L*
- AST (serum aspartate aminotransferase) aka SGOT
  - Normal range: 5-40 U/L*
- Alkaline Phosphatase (ALP or Alk Phos)
  - Normal range: 30-120 U/L*
- Total Bilirubin (majority of circulating is unconjugated)
  - Normal range: <1.2 mg/dL adults; <1.0 mg/dL <18*

*normal ranges may vary depending on lab/institution
SGPT: serum glutamic-pyruvic transaminase; SGOT: serum glutamic-oxaloacetic transaminase

Kwo P, Cohen S, Lim J. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol* 2017; 112:18-35; doi: 10.1038/ajg.2016.517; published online 20 December 2016. https://www.emedicinehealth.com/liver_blood_tests/article_em.htm

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Key Points

- Liver chemistries are markers of liver injury and include:
  - **ALT** (present primarily in liver = more specific marker for hepatocellular injury)
  - **AST** (present in liver, cardiac muscle, kidney, brain, skeletal muscle)
    - Elevated AST with normal ALT think cardiac or muscular injury
  - **Alk Phos** (present in liver, bones, kidney, intestine and placenta)
    - If elevated ordering a fractionated alk phos can distinguish between hepatic vs bone
    - Hepatic can be confirmed with GGT (gamma-glutamyl transferase)
  - **Bilirubin** (present in liver, by-product of red blood cell breakdown)
    - Circulates as unconjugated bilirubin
    - Conjugated in liver – makes it water soluble – excreted into bile
    - Elevated conjugated bilirubin indicates hepatocellular dysfunction or cholestasis

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Key Points *(continued)*

- Liver function includes:
  - Albumin
  - Bilirubin
  - Prothrombin time
- “LFTs” (liver function tests) by itself is technically a misnomer. When referring to AST/ALT/Alk Phos they are “LCTs” (liver chemistry tests)

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Case Study - Chuck

- 50-year-old male, truck driver
- Here for his follow-up after DOT physical, told to see PCP to discuss lab results
- History: Knows he has gained weight – eats fast food on the road, no exercise
- Meds: Can’t take NSAIDs due to history of ulcer so takes acetaminophen nightly for back pain. Started taking supplements from his wife to help with energy and weight loss (doesn’t know what’s in it)
- SHx: Doesn’t drink during his trips but will often have a 12 pack PBRs “cold brewskies” while watching the football game with his buddies. Denies history of illicit drug use (including no IV drug abuse)

SHx: Social History

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Chuck’s Exam

- Vitals: BP 142/88, BMI 46
- Pex: notable for central obesity, technically difficult exam due to body habitus however no obvious signs of significant liver disease (i.e., no jaundice, ascites, etc.) and no tenderness on exam
- Multiple tattoos on arms and chest that he got while serving overseas in the military
- Labs from DOT exam

AST 56	Total chol 230
ALT 64	LDL 132
Alk phos 60	TG 204
Total bili 1.0	FBS 105
CBC normal	

Pex: Physical Examination

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Toxins

- Don't forget the liver is the first stop in the body
- Many substances (especially when taken in excess or in combination with other substances) can *stress the liver*
- Examples:
  - Acetaminophen
  - Alcohol
  - Supplements
  - Prescription medications
    - Statins
    - Antibiotics
    - Antiepileptics
    - Some NSAIDs
    - antiTB meds
    - Antiretrovirals
    - Biologics
    - Chemotherapeutic agents
    - Combo analgesics

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Alcohol – But it's Healthy for my Heart . . . Right?

- Independent risk factor but also contributor in somebody with chronic liver disease due to other causes
- Labs: AST:ALT (2:1), if (3:1) further increases likelihood of liver disease, GGT used to identify patterns of alcohol abuse
  - "Scotch & Tonic" (AST > ALT think alcohol)
- How much is too much?
  - NIAAA (National Institute on Alcohol Abuse and Alcoholism) defines heavy drinking as follows:
    - Men: consuming more than 4 drinks on any day or more than 14 drinks per week
    - Women: consuming more than 3 drinks on any day or more than 7 drinks per week
  - NIAAA defines standard drink as follows:
    - 11-14 g of alcohol = 1 drink
    - 1 drink = 40% spirit = 1 glass of wine = 1 12-ounce beer
- "Safe" daily intake should not be more than 2 drinks
  - Applies to healthy people

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Supplements “But they are natural!”… So is Arsenic

Herbal/Supplement	Claims
Chaparral	Antioxidant, weight loss, liver wellness, improved immunity, treatment for skin disorders
Echinacea	Treating and preventing common cold and URIs
Ji Bu Huan	Chinese Herb – insomnia, arthritic/orthopedic pain, GI complaints
Garcinia Cambogia	Weight loss
Germander	Herbal teas for centuries – recently marketed for weight control, management of DM, hyperlipidemia
Green Tea Extract	Antioxidant activity, prevent cancer and heart disease, promote weight loss, decrease periodontal disease, treat C diff.
Kava kava	Insomnia, anxiety
Niacin	Raise HDL, lower LDL (cardiac benefit?)

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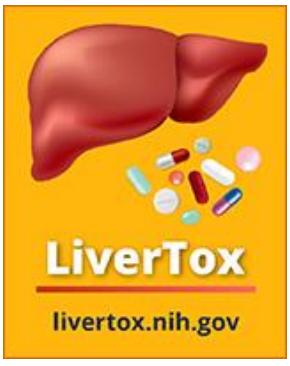
Good Resource for Clinicians



Great resource for clinicians to look up common medications, herbals, supplements.

Provides information on whether these products have been shown to cause liver injury, but also if they have NOT been shown to affect the liver.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/

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NSAIDS?
But I thought they were metabolized through the kidneys?

- Liver injury from NSAIDs is rare (1-10 cases per 100,000 prescriptions) and typically seen within 1-3 months of starting the medication
- Uncommon, however due to the large volume of people that take NSAIDS (over 30 million Americans) important to consider
- Multiple NSAID withdrawn from use/testing due to hepatotoxicity
- Current NSAIDs that have higher risk: sulindac, diclofenac
- Take Home Point – Should consider . . .

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Nonsteroidal Antiinflammatory Drugs (NSAIDs) [Updated 2020 Mar 18]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548614/

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Viral Hepatitis

- Hep A, B, C testing
- Other viral causes you may consider testing:
  - Cytomegalovirus (CMV)
  - Epstein-Barr virus (EBV)
  - Hep D, E
- Hep A
  - Doubtful in Chuck – asymptomatic – but usually included in panel
  - Hep A IgM
  - After Hep A vaccination became available in 1995 – US cases dropped by 95%
  - Fecal/oral transmission

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Hepatitis B

- 1.5 million Americans with chronic Hep B
- 280 million worldwide
  - Asia/Africa “endemic”
    - Vertical or Horizontal transmission (i.e., mom to baby or person-person)
  - US/Western Nations
    - Parenteral (IV) or Sexual Transmission
- 3 serologic tests
  1. HBsAg (Surface antigen) – indicative of infection
  2. HBcAb (Core antibody) – indicative of prior exposure to disease
  3. HBsAb (Surface antibody) – indicative of immunity to infection (either natural or vaccination)
     - Chronic infection confirmed by HBsAg and/or positive viremia (HBV DNA assay – highly sens)
     - Confirmation of infection – refer to hepatologist

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Hepatitis C

- 4.1 million Americans positive for antibodies for Hep C
  - 3 million with positive Hep C RNA (ie, infectious)
- Universal Hep C screening:
  - Once in a lifetime for all adults 18+ (regardless of lab values)
  - All pregnant women, HIV, ever injected drugs/shared needles, hemodialysis, persistent abnormal ALT, prior blood transfusion/organ transplant, needle stick and tattoos
- Hep C antibody
  - Sensitivity 92-97%
  - If + confirm: highly sens HCV RNA PCR assay (hi sens/spec)
  - If +RNA refer to hepatologist or initiate Hep C treatments (see guideline link below)
  - www.hcvguidelines.org

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Total Bilirubin 2.6!!! . . . Is This Significant?

- Isolated elevated total bilirubin in the absence of signs and symptoms of liver disease or any other liver chemistry abnormalities – consider **Gilbert’s syndrome**
- AKA Gilbert-Meulengracht syndrome
- Hereditary condition (5-10% of Western European populations)
- Intermittent unconjugated hyperbilirubinemia
- Hepatocellular disease and hemolysis are absent
- No additional work-up indicated

VanWagner LB, Green RM. Evaluating elevated bilirubin levels in asymptomatic adults. *JAMA*. 2015;313(5):516-517. doi:10.1001/jama.2014.12835

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NAFLD: Nonalcoholic Fatty Liver Disease

- Highly prevalent - approx 24% of US
  - Higher in Hispanics
  - Lower in Blacks
- 1.43 increased risk of mortality
- Occurs from an accumulation of excess fat (primarily triglycerides) being stored in the liver cells
- Includes spectrum of:
  - Simple steatosis
  - NASH (nonalcoholic steatohepatitis) – highest risk of progression to cirrhosis and hepatocellular carcinoma (HCC)
    - Characterized by inflammation with progression to fibrosis
  - Fibrosis
- Associated with obesity, metabolic syndrome, diabetes, dyslipidemia, hypertension

Kwo P, Cohen S, Lim J. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol* 2017; 112:18-35; doi: 10.1038/ajg.2016.517; published online 20 December 2016. Arshad T, Golabi P, Henry L, Younossi ZM. Epidemiology of Non-alcoholic Fatty Liver Disease in North America. *Curr Pharm Des*. 2020;26(10):993-997. doi: 10.2174/1381612826666200303114934. PMID: 32124690.

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How Do We Know if it’s NASH?

- Suspected dx of NAFLD often seen on liver ultrasound *aka fatty liver* but that doesn’t necessarily mean that the patient has NASH
- NASH is a subset of NAFLD
  - Fatty liver on ultrasound, or other imaging (CT/MRI) PLUS the presence of abnormal liver chemistry tests – highly suggestive of NASH
- To assess the presence of fibrosis in NASH:
  - Liver biopsy “Gold Standard”
  - Vibration controlled transient elastography scan (ultrasound or MRI)
  - Blood test to assess fibrosis-serum biomarker to assess fibrosis in patients with chronic Hep B or C, alcoholic liver disease and metabolic steatohepatitis
  - Noninvasive tools to determine presence and severity of fibrosis

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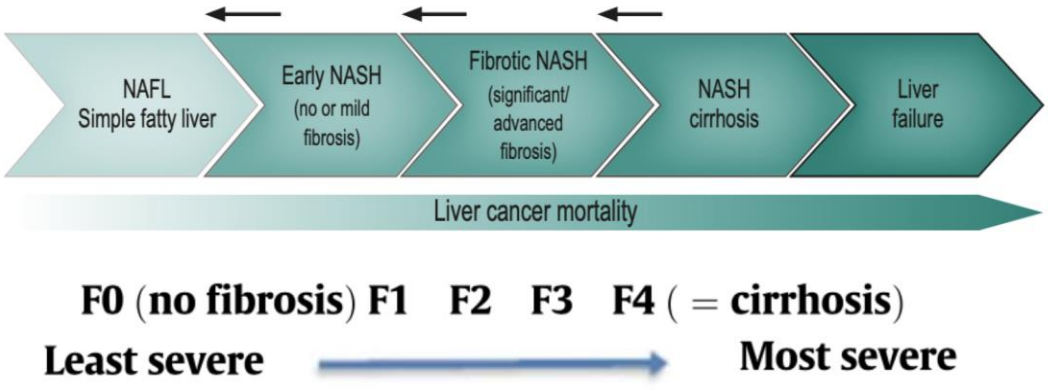
Progression of NASH



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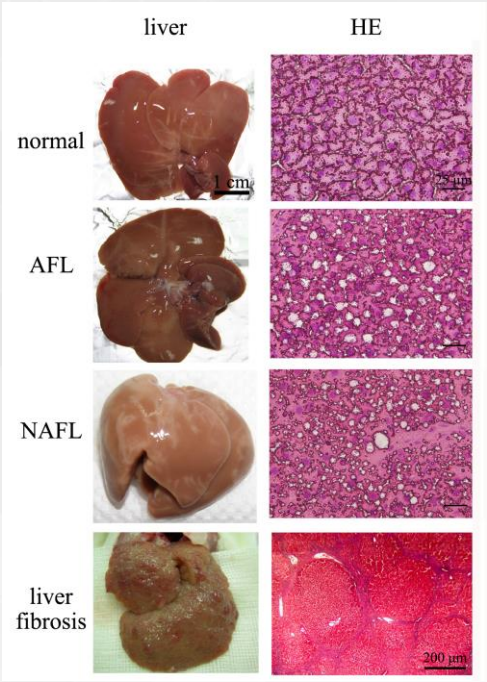

Liu, SL., Cheng, CC., Chang, CC. *et al.* Discovery of serum biomarkers of alcoholic fatty liver in a rodent model: C-reactive protein. *J Biomed Sci* 18, 52 (2011). https://doi.org/10.1186/1423-0127-18-52. Figure available via license: Creative Commons Attribution 2.0 Generic

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Is Any of This Reversible?

- Yes! NASH, at almost every stage in the evolution there is opportunity for reversal (up until fulminate liver failure)
- Lifestyle modifications and treating coexisting comorbid conditions, both of which contribute to the development of NAFLD and potentially NASH, can reverse the toxic deposition of fatty molecules in the liver
  - Aggressive weight loss (including considering bariatric surgery)
  - Tightening diabetic control
  - Lowering BP and cholesterol (especially TGs)
  - Exercise
  - Toxin reduction (such as alcohol, liver-toxic medications/supplements)

Lassailly G, Caiazzo R, Buob D, et al. Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. *Gastroenterology*. 2015 Aug;149(2):379-88; quiz e15-6. doi: 10.1053/j.gastro.2015.04.014. Epub 2015 Apr 25. PMID: 25917783.

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Impact of Weight Loss on Liver Improvement

% Weight Reduction	Impact on Liver
5%	Reduces liver fatty deposition
7-10%	Improvement of liver inflammation
>10%	Improvement of fibrosis and scaring

- Therefore, the target weight loss of 7-10% is if you have overweight or obesity with NAFLD
- No magic diet (low carb tends to be equivalent to low fat) if 7-10% loss achieved and maintained

Musso, G., Cassader, M., Rosina, F. *et al.* Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* 55, 885–904 (2012). https://doi.org/10.1007/s00125-011-2446-4

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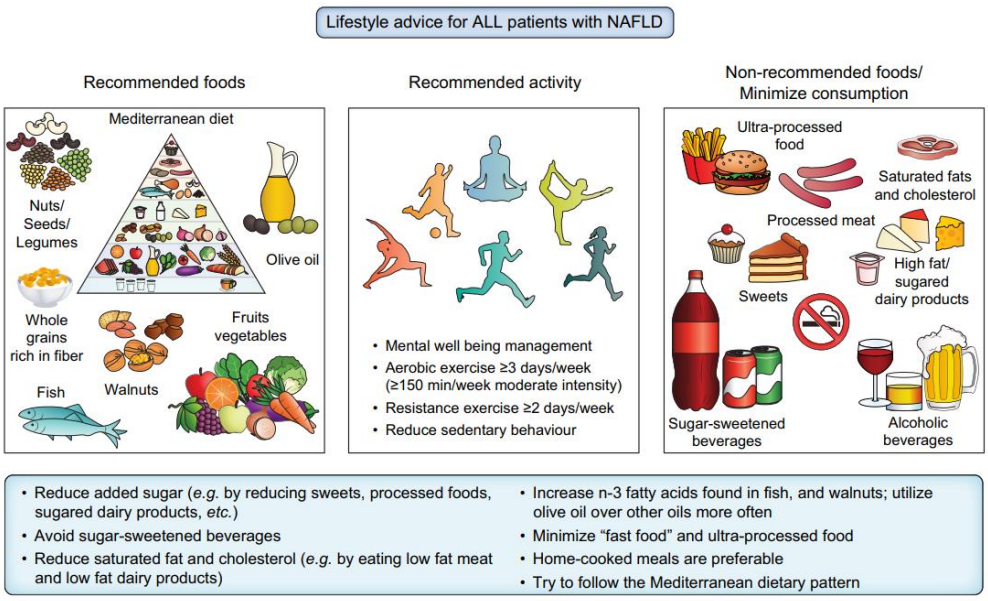

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Medications to Treat NASH?

Currently, no FDA approved medications to treat NASH specifically. Some medications that are used to treat other medical conditions have been shown to have possible efficacy based on improvement seen on liver biopsy.

“Medications”	Effect
Vitamin E 800 IU	PIVENS TRIAL: showed promise (possibly due to anti-cellular death and antioxidant properties) but only in patients without cirrhosis and without DM, however no significant effect on fibrosis *Caution – long term use potentially increases risk of prostate cancer
Pioglitazone 45mg QD	Reduced liver chemistries, steatosis, liver cell damage and inflammation Recent global analysis of multiple studies – showed resolution of NASH, scar tissue *Caution - some weight gain, increased risk of non-osteoporotic fx, bladder cancer
GLP1 – RA Liraglutide 1.8mg daily Semaglutide 2.4mg weekly	NASH resolved significantly compared to placebo, improvement of fibrosis stage, higher doses of semaglutide 2.4mg weekly (resolution occurred more frequently and higher fibrosis improvement)

Lassailly G, Caiazzo R, Buob D, et al. Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients. *Gastroenterology*. 2015 Aug;149(2):379-88; quiz e15-6. doi: 10.1053/j.gastro.2015.04.014. Epub 2015 Apr 25. PMID: 25917783. Francque S., Marchesini G., Kautz A., et al. Non-alcoholic fatty liver disease: A patient guideline.

https://easl.eu/wp-content/uploads/2021/09/Non-alcoholic-fatty-liver-disease-A-patient-guideline-final.pdf. Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med* 2021;384:1113-24. 10.1056/NEJM

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How Do We Monitor?

- NAFLD
  - No consensus on frequency of monitoring – experts recommend at least every 2-5 years with imaging
  - If higher risk (i.e., comorbid conditions – obesity, DM, etc.) frequency of monitoring may need to be yearly (discuss with PCP/specialist)
- NASH (management with specialist)
  - With below F2 fibrosis: monitoring at least yearly (if comorbid dz Q6 months?)
  - With significant fibrosis F2 and higher (i.e., severe inflammation): monitoring every 6 months
  - With cirrhosis: monitoring every 3-6 months
  - Monitoring includes blood tests, ultrasound, elastography

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Summary of Causes to Consider

HEPATIC (TYPICALLY: ALT>AST)

- NAFLD
  - Steatosis
  - NASH
- Chronic viral hepatitis
- Acute viral hepatitis
- Medications and drug-induced liver injury
  - Prescription medications
  - Herbal products and supplements
  - Over-the-counter agents
- Toxic hepatitis (amanita exposure)
- Hemochromatosis
- Autoimmune hepatitis
- Wilson’s disease
- Alpha-1-antitrypsin deficiency
- Celiac disease
- Acute bile duct obstruction
- Liver trauma
- Post-liver surgery
- Veno-occlusive disease/sinusoidal obstruction syndrome
- Diffuse infiltration of the liver with cancer
- HELLP syndrome
- Acute fatty liver of pregnancy
- Sepsis
- Hemophagocytic lymphohistiocytosis

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Summary of Causes to Consider

HEPATIC (TYPICALLY: AST>ALT)

- Alcoholic liver disease
- Cirrhosis (of any etiology)
- Ischemic hepatitis
- Congestive hepatopathy
- Acute Budd-Chiari syndrome
- Hepatic artery damage/ thrombosis/occlusion
- Total parenteral nutrition (TPN)

NON-HEPATIC

- Skeletal muscle damage/ rhabdomyolysis
- Cardiac muscle damage
- Thyroid disease
- Macro-AST (Immunoglob bound AST)
- Strenuous exercise
- Heat stroke
- Hemolysis
- Adrenal insufficiency

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Algorithm for Evaluation of AST and/or ALT Level

BORDERLINE ELEVATION <2x ULN	MILD ELEVATION 2-5x ULN
• History/Physical Exam • Discontinue hepatotoxic meds/alcohol consumption • Assess for risk factors for fatty liver and viral hepatitis	• History/Physical Exam • Discontinue hepatotoxic meds/alcohol consumption • Assess for risk factors for fatty liver and viral hepatitis
• CBC/platelet count, AST/ALT, Alk Phos, TB, albumin, PT/INR • HBsAg, HBcAb, HBsAb, HCV Ab with PCR confirmation if +, iron panel, abdominal ultrasound	• CBC/platelet count, AST/ALT, Alk Phos, TB, albumin, PT/INR • HBsAg, HBcAb, HBsAb, HCV Ab with PCR confirmation if +, iron panel • Abdominal ultrasound
• If negative, consider observation for **3-6 mos** with repeat AST/ALT, Alk Phos, TB or …	• If negative, consider observation for **3 mos** with repeat AST/ALT, Alk Phos, TB or continue investigation
• If persistently elevated, continue investigation: ANA, ASMA, gamma-globulin, ceruloplasmin, alpha-1 antitrypsin phenotype and may consider additional tests based on history (celiac sprue, tick-born disease, thyroid disease, muscle disorders)	• If persistently elevated, continue investigation: ANA, ASMA, gamma-globulin, ceruloplasmin, alpha-1 antitrypsin phenotype and may consider additional tests based on history (celiac sprue, tick-born disease, thyroid disease, muscle disorders) • If no diagnosis, consider diagnostic liver biopsy
• If normal, further testing at discretion of clinician or refer to hepatologist for consideration of liver biopsy	

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Case Study – Our Plan for Chuck

1. Order additional laboratory testing including a repeat hepatic panel and hepatitis panel
2. Instruct Chuck to discontinue all supplements and acetaminophen
3. Refrain from all alcohol
4. Aggressive weight loss (consider anti-obesity meds)
5. Increased physical activity
6. Order further imaging
7. If repeat liver chemistries are still elevated and ultrasound shows presumptive fatty liver – proceed with elasticity scan
8. Depending on elasticity score – determine interval for follow-up and/or referral to specialist

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Summary

- The liver is the filtration system for materials ingested by the body
- Its primary function includes processing of nutrients and toxins
- AST/ALT/Alk Phos/Bilirubin are “liver chemistries” whose abnormal values indicate liver injury
- There are multiple etiologies for abnormal liver chemistries (including toxins, infectious diseases, autoimmune, cancer, NAFLD/NASH)
- NAFLD is highly prevalent and an increasing public health issue
- NASH (a subset of NAFLD) carries a high risk of progression to cirrhosis
- Several common medical comorbidities increase the risk of NAFLD and progression to NASH
- Lifestyle modifications in conjunction with disease management can reverse progression of fibrosis due to NASH

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