A Rational Approach to the Patient with Abnormal LFTs

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Learning Objectives

• Review the types of LFTs.
• Understand the different patterns of LFTs in liver disease.
• Understand how to use those patterns to best direct a clinical evaluation.
Liver Function Tests (LFTs)

• Tests to assess liver function
  – Bilirubin
  – Albumin
  – Prothrombin Time

• Tests to detect liver injury – liver enzymes
  – Aminotransferases
    • Alanine aminotransferase (ALT or SGPT)
    • Aspartate aminotransferase (AST or SGOT)
  – Alkaline phosphatase
  – Gamma glutamyltransferase (GGT)
Shortcomings of LFTs

• They lack sensitivity, particularly in chronic liver disease
  √ Some patients with chronic HCV, HBV and even cirrhosis can have normal aminotransferases

• They lack specificity
  1 All three are found in other organs
     • AST: liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes…
     • ALT: more liver specific than AST
     • ALP: liver, bone, small intestine, placenta
Using LFTs to guide the evaluation of the patient

• Are the elevations acute or chronic?
• Is the patient symptomatic?
• What is the pattern and degree of elevation?
  – Hepatocellular injury
    • Marked increase in the ALT and AST
    • Lesser increase in alkaline phosphatase
  – Cholestatic injury
    • Marked increase in the alkaline phosphatase
    • Lesser increase in the ALT and AST
  – The bilirubin is not helpful differentiating between the two
Evaluation of the patient with an isolated hyperbilirubinemia

- Fractionate the bilirubin

  - ≥15% direct often >50%
    - Dubin-Johnson or Rotor’s syndrome
  - <15% direct
    - Evaluate for hemolysis: haptoglobin, LDH, peripheral blood smear
      - Evaluation negative
        - Review drugs (e.g. ribavirin, rifampin, probenecid)
          - No culprit medications
            - Inherited disorders: Gilbert’s or Crigler-Najjar syndromes, types 1 or 2
      - Evaluation positive
        - Hemolytic disorder
Case 1

• A previously healthy 25-year-old man presents with nausea, profound fatigue, and then jaundice.
• ALT 1523 U/L (normal 0-42) and AST 1118 U/L (0-40)
• Alkaline phosphatase 130 U/L (0-120)
• Total bilirubin 10.2 mg/dl (0.4-1.2)
Case 1 - Interpretation

• Acute, hepatocellular injury
• That impression, plus the degree of elevation of the aminotransferases and the patient’s symptoms, suggests a limited number of possible diagnoses that should guide the evaluation:
  — Viral hepatitis
    • Asking about exposures (HBV, HCV) and recent travel (HAV, HEV)
  — Toxic insult
    • Prescribed and OTC medications, herbals, supplements
  — Ischemic injury
Question 1

An appropriate test in this case is:

A. Hepatitis A IgM antibody
B. Hepatitis B core IgG antibody
C. Hepatitis C DNA
D. Hepatitis D antibody
E. Hepatitis E IgG antibody
Case 1 – appropriate diagnostic testing

- **Testing for acute viral hepatitis:**
  - **Hepatitis A**
    - HAV IgM
  - **Hepatitis B**
    - HBsAg, HBsAb, HBV DNA, HBcAb IgM
    - Remember the window period between surface antigen and antibody positivity
  - **Hepatitis C**
    - HCV RNA
    - HCV Ab takes 6+ weeks to turn positive
  - **Hepatitis E**
    - HEV IgM
- **Diagnosis: acute HAV**
Case 2

• A previously healthy 55-year-old man presents with jaundice
  
  – Other complaints: recent onset abdominal/back pain

• ALT 80 U/L (0-42) and AST 94 U/L (0-40)

• Alkaline phosphatase 660 U/L (0-120)

• Total bilirubin 6.6 mg/dl (0.4-1.2)
Evaluation of the patient with cholestatic liver enzymes

Bile ducts not dilated: intrahepatic cholestasis

AMA, ACE level
Viral serologies: HAV, HBV, HCV
EBV, CMV

Review drug list
RUQ US

Bile ducts dilated: extrahepatic cholestasis

CT scan
MRI/MRCP

AMA+
Evaluation negative

Consider liver biopsy

MRCP
Liver biopsy

ERCP +/- EUS
Case 2 - Interpretation

- Acute (subacute), cholestatic injury
- Next step in the evaluation is to determine if this is intra- or extrahepatic cholestasis
  - Assess for biliary dilation:
    - Its presence indicates large duct obstruction
  - Choice is either ultrasound or CT
Question 2

The most likely diagnosis in this case is:

A. Acute cholecystitis
B. Mass in the pancreatic tail
C. Cholelithiasis
D. Choledocholithiasis
E. Cholangiocarcinoma
ERCP: Endoscopic retrograde cholangiopancreatography

Diagnosis: Cholangiocarcinoma of the distal common bile duct.

Plan: Surgical resection.
Abnormal liver enzymes in the asymptomatic patient:

- A diagnosis/etiology can be identified non-invasively in the majority of patients
- Appropriate and cost-effective testing can and should be guided by the pretest probability of specific forms of liver disease – a determination made in part by a carefully performed history
The history

• It is critical to ask specifically about the use of:
  – Medications, prescribed or OTC, and when they were started
  – Vitamin preparations and supplements
  – Complementary and alternative medical (CAM) therapies
  – Drugs, now or in the past, parenteral or otherwise
  – Alcohol
The prevalence of herbal usage in the U.S.

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<td>2005</td>
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Muscle cramps are a common complaint in patients with cirrhosis

“When taken as directed, Valerin is 100% safe.”

Each tablet contains:
6 parts Valerian Root

“For relief of muscle spasms, tension, and stress.”
CAM and Liver Disease
## Liverite Liver Aid - Ingredients

### Supplement Facts

**Serving Size:** 2 capsules  
**Servings Per Container:** 75  

### Ingredients:

<table>
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<th>Ingredient</th>
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<th>% Daily Value**</th>
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<tr>
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<td>2. Proprietary Blend</td>
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<td>- Liver Hydrolysate with 17 amino acids</td>
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<td>- Choline (bitartrate)</td>
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<tr>
<td>- Inositol</td>
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<td>- L-Cysteine</td>
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<td>- Phosphatidylcholine</td>
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<td>- Phosphatidylinositol</td>
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<td>- Choline (lecithin)</td>
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<td>3. Milk Thistle Extract</td>
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**Percent Daily Value is based on a 2000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.**

† Daily Value not established.
The history

• Other important points:
  – Other exposures:
    • Blood transfusions
    • Tatoos/piercings
  – Social history: ethnicity
  – Family history:
    • Liver disease
    • Autoimmune diseases
  – Directed ROS – examples:
    • Joint pains, skin changes, symptoms of hyperglycemia (HHC)
    • SICCA symptoms, pruritus (PBC)
Laboratory evaluation of elevated aminotransferases: step 1

Goal is to identify treatable forms of liver disease

• Testing:
  – Hepatitis B and C
  – Non-alcoholic fatty liver disease (NAFLD)
  – Hereditary hemochromatosis (HHC)
  – Autoimmune hepatitis
  – Wilson’s disease*

* Depending in part on patient characteristics
Evaluation of elevated aminotransferases: step 2

• Testing:
  - Goal – identify non-hepatic causes of elevated aminotransferases
    • Muscle disorders
    • Thyroid disorders
    • Celiac disease
  - Goal – identify rarer hepatic causes of elevated aminotransferases
    • Alpha-1-AT deficiency
Case 3

• 54-year-old man had LFTs checked as part of a routine physical:
  - ALT 411, AST 179, ALP 81 and T. bili 0.7
  - Albumin 4.7, INR 1.1

• LFTs repeated over three months

• No complaints
Evaluation of the patient with elevated aminotransferases

History
Review medications including OTC drugs, CAM, alcohol, illicit drug use

Stop potential toxins
Follow LFTs

History unrevealing or no response to stopping potential hepatotoxins

HCV Ab
HBsAg, HBsAb, HBeAb
Iron, TIBC (Ferritin)
ANA, SMA, SPEP
Ceruloplasmin (age<40)
RUQ US

HCV RNA
HCV genotype

Liver biopsy

HBsAg+

HBeAg, HBeAb
HBV DNA

Liver biopsy

ANA+ and/or SMA+
Globulins

Ceruloplasmin

Evaluation unrevealing

Steatosis on US

Iron saturation > 45%

Ferritin
HFE gene testing +/- liver biopsy

Recommend weight loss
Follow LFTs

Evaluation unrevealing

Liver biopsy if aminotransferase levels > 2 times ULN

Ophthalmoscopic exam
24 hour urine for copper
Liver biopsy

HCV RNA
A1AT phenotype
CK and aldolase
TFTs
TTG antibody

Evaluation unrevealing
Case 3

• PMH:
  - Stage 2 squamous cell CA of tongue treated with chemo/XRT 4 years ago
  - Periodic abnormal LFTs during treatment
  - HTN
  - Hypothyroidism
  - No transfusions
  - Self-limited hepatitis in the 1970’s while traveling across the country with friends

• Medications:
  - Prescribed: levothyroxine
  - OTC: calcium, vitamin C
  - CAM: no herbals or supplements
Case 3

• Habits:
  – Occasional EtOH
  – No drug use of any form

• SH:
  – Engineer without job exposures
  – Italian descent

• FMH: No liver disease
Case 3

- HCV Ab: positive
- HBsAg: negative; HBsAb: positive; HBcAb positive
- Iron: 116
- TIBC: 378
- Ferritin: 227
- Ultrasound: no HSM, no fat
- ANA positive at 1:160
- SMA negative
- Gamma globulins normal
Case 4

- 55-year-old woman with asymptomatic elevation of her aminotransferases:

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Case 4

- **PMH:** HTN, osteoporosis, squamous cell CA of skin, no transfusions
- **Medications:**
  - Prescribed: atenolol, HCTZ
  - OTC: Claritin, ASA
  - CAM: no herbals or supplements
- **Habits:** Glass of wine per night, occasionally 2 or more. No drug use of any form.
- **SH:** Married. Northern European, predominantly Irish descent
- **FMH:** No liver disease
Case 4

- HCV Ab: negative
- HBsAg, HBsAb, and HBcAb: negative
- Iron: 259
- TIBC: 262
- Ferritin: 2401
- US: No fatty infiltration
- ANA negative
- SMA negative
Case 5

• 18-year-old woman:
  — ALT 250, AST 190, normal ALP and T bili
  — Albumin 4.0, INR 1.0

• Labs done at the time of a routine physical

• Only complaint: fatigue.
Case 5

• PMH: None

• Medications:
  — Prescribed: none
  — OTC: topical acne medications, PRN NSAIDs
  — CAM: no herbals or supplements

• Habits: rare EtOH. No drug use of any form.

• SH: Single. Student. + multiple body piercings.

• FMH: No liver disease. Aunt with SLE.
Case 5

- HCV Ab: positive
- HBsAg, HBsAb, and HBcAb: negative
- US: No fatty infiltration.
- ANA positive at 1:320
- SMA positive at 1:160
- Gamma globulins: 3.0 gm/dL (top normal 1.6 gm/dL)
- Ceruloplasmin: 28 (normal: 20-60)
- HCV RNA negative
Question 3

A 57-year-old woman from Bulgaria is found to have elevated serum aminotransferases (~2 times the ULN) that persist over 6 months. Which of the following testing is not indicated?

A. HBsAg
B. HCV Ab
C. Ceruloplasmin
D. Iron and TIBC
E. ANA
Case 6

- 67-year-old woman:
  - Mildly elevated ALP (<1.5 times the ULN) dating back to at least 1997.
  - Transaminases and T bili normal

- Only complaint: joint aches attributed to OA.
Evaluation of the patient with an isolated elevation of the alkaline phosphatase

Either: Fractionate ALP or GGT or 5' NT level

Bone origin

Bone evaluation

Liver origin

Review drug list
AMA
ACE level
RUQ US

Bile ducts dilated

CT scan
MRI/MRCP

AMA+

ACE level elevated

Consider liver biopsy

Evaluation unrevealing

ERCP +/- EUS

Bone origin

Bone evaluation

Liver origin

Review drug list
AMA
ACE level
RUQ US

Bile ducts dilated

CT scan
MRI/MRCP

AMA+

ACE level elevated

Consider liver biopsy

Evaluation unrevealing

ERCP +/- EUS

Bone origin

Bone evaluation

Liver origin

Review drug list
AMA
ACE level
RUQ US

Bile ducts dilated

CT scan
MRI/MRCP

AMA+

ACE level elevated

Consider liver biopsy

Evaluation unrevealing

ERCP +/- EUS
• PMH: HTN, OA, hypercholesterolemia, type 2 DM

• Medications:
  — Prescribed: Crestor, ASA, glucophage, omeprazole, Tenoretic, Zestril, Norvasc, indomethacin, glyburide
  — ALP elevation predated all medications
  — OTC: Denies
  — CAM: no herbals or supplements

• Habits: rare EtOH. No drug use of any form.


• FMH: No liver disease. Sister with arthritis.

• PE: 5’0”, 205 pounds, BMI 40
Isolated ALP elevation

• First step – verify the source of the ALP
  — Fractionate the ALP: “ALP liver in origin”
  — GGT or 5’ nucleotidase: GGT elevated

• Second step:
  — RUQ imaging: “probable fatty liver, bile ducts normal”
  — AMA: +1:80

• Third step:
  — Liver biopsy: Mild to moderate steatosis, stage 1-2 primary biliary cholangitis (PBC)
Final Case

• 38-year-old man presents to his local ER with jaundice
• A friend noticed his eyes were yellow
• Initially asymptomatic, but developed pruritus and nausea
• AST 194, ALT 420, ALP 141, T bili 16.0
  — Amylase and lipase both mildly elevated
Final Case

- PMH: none
- Medications:
  - Prescribed: none
  - OTC: topical acne medications, PRN NSAIDs
  - CAM: denies herbals and supplements
- SH: Married. No tobacco or drugs. Occasional EtOH.
- PE: Thin. 5’5”, 140 pounds. Exam unremarkable. No stigmata of chronic liver disease.
Final Case

- HCV Ab: negative
- HBsAg, HBsAb, and HBcAb: negative
- Iron 110, TIBC 350
- Ferritin 150
- US: multiple gallstones, no biliary dilation
- ANA and SMA negative
- Gamma globulins: 1.8 gm/dL (top normal 1.6 gm/dL)
- Ceruloplasmin: 26

Personal trainer at Bally Total Fitness.
Final Case

• Started “Methyl masterdrol” approximately 2 months ago

Are you satisfied we have the answer?

“Explosive Strength”

www.beyondmuscle.com
MRI/MRCP: performed for the elevated amylase/lipase and gallstones
Stauffer’s Syndrome

• Nonmetastatic nephrogenic hepatic dysfunction syndrome
  – Originally described in 1961 (Gastro 1961;40:694)
  – Anicteric cholestasis
    • Elevated ALP and GGT with HSM
    • IL-6 overproduction by the tumor has been implicated

• Icteric cholestasis is a rare variant
  – 4 cases in the literature
  – All presented with painless jaundice, incidentally found renal masses, and resolution of jaundice with surgery
“I’d rather be lucky then good.”

Lefty Gomez