Approach to the Patient with Abnormal Liver Enzymes

Donald Gardenier, DNP, FNP-BC

Assistant Professor and Clinical Program Director

Icahn School of Medicine at Mount Sinai
New York, NY
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Overview

Yes:
1. Review of clinical labs and their significance
2. Usual patterns seen in major liver diseases
3. Brief review of the major liver’s major functions
4. Brief review of major liver diseases
5. Focused on primary care
6. Interactive

No:
1. In-depth physiology
2. Urgent management
3. How to manage particular liver diseases
Liver Functions

- Protein synthesis
- Cholesterol synthesis
- Metabolic/catabolic functions
  - Bile synthesis and transport
- Detoxification
- Factor production
Liver-Related Blood Tests

- Markers of hepatocyte injury
  - Serum aminotransferases
    - Aspartate aminotransferase (AST)
    - Alanine aminotransferase (ALT)
  - \( \gamma \)-glutamyltransferase (GGT)
  - Alkaline phosphatase (AP)
    - Liver
    - Bone
  - 5’-nucleotidase (5’-NT)*
Liver-Related Blood Tests

- Test of liver metabolism
  - Total bilirubin

- Tests of liver synthetic function
  - Serum albumin
  - Prothrombin time
Serum Fibrosis Markers

- Indicators of fibrosis/cirrhosis
- All have limitations
- FIB-4 Score:
  - \((\text{AGE} \times \text{AST}) / (\text{platelets} \times \sqrt{\text{ALT}})\)
  - >3.25 sensitive and specific for significant fibrosis
- APRI = AST: Platelets ratio
  - \(\text{AST/ASTULN/Platelets}\)
  - \(\geq 1\) significant fibrosis likely
- FibroSure
  - >72 significant fibrosis likely
Aminotransferases

- Formerly called transaminases
- Included in most routine blood tests
- Found in:
  - Liver
  - Cardiac muscle
  - Skeletal muscle
  - Kidneys
- ALT is more specific to the liver
- ALT and AST normally present at low levels
  - Usually < 30 – 40 u per liter
  - Normal ranges vary widely
  - Sometimes not adjusted for gender
Aminotransferases

- Normal range is calculated as follows:
  - mean of a group of healthy persons
  - +/- 2 standard deviations
  - 5% of the results fall outside the normal range
  - 2.5% may be >upper level of normal (ULN)
- An abnormal result may not be indicative of disease
- Frequently leads to the diagnosis of liver disease
- Requires a subjective/objective evaluation
- Damage to cell membrane causes release into serum
  - Necrosis of hepatocyte not required
  - Poor correlation between level and degree\(^1\)

\(^1\)Pratt 1999
Aminotranferases

- Air force trainee volunteer blood donors (n = 19,877)\(^1\)
  - 99 (0.5%) had ALT elevations
  - Etiology was determined in 12 (12%)
    - 4 each = hepatitis B; hepatitis C
    - 2 = autoimmune hepatitis
    - 1 each = cholelithiasis; acute appendicitis

- Consecutive blood donors with elevated ALT (n = 100)\(^2\)
  - 48% = alcohol related
  - 22% = fatty liver
  - 17% = hepatitis C
  - 4% = other
  - 9% = no etiology determined

\(^1\)Kundrotas 1993
\(^2\)Katkov 1991
Aminotransferases

- Elevated ALT with subsequent biopsy (n = 149)³
  - 56% = fatty liver
  - 20% = hepatitis C
  - 11% = alcoholic liver disease
  - 3% = hepatitis B
  - 8% = other causes
  - 2% = no etiology

- Chronic aminotransferase elevations (n = 1124)⁴
  - 81 (7%) = no etiology found; biopsied
    - 41 (50%) = steatosis
    - 26 (32%) = steatohepatitis
    - 4 (5%) = fibrosis
    - 2 (2%) = cirrhosis
    - 8 (12%) = normal histology

³Hultcrantz 1986
⁴Daniel 1999
Causes of Elevated Aminotransferases

- Liver-related
  - Alcohol use
  - Viral hepatitis
  - Medication
  - Fatty infiltration
  - Autoimmune hepatitis
  - Hemochromatosis
  - Wilson’s Disease
  - $\alpha_1$-antitrypsin deficiency

- Extrahepatic causes
  - Celiac sprue
  - Muscle metabolism disorders
  - Acquired muscle disorders
  - Vigorous exercise


\textbf{\textit{\(\gamma\)-Glutamyltransferase}}

- Present in the liver and other tissues
- Sensitive to bile ducts and/or liver
- Lacks specificity
  - Elevations associated with:
    - Diabetes
    - Hyperthyroidism
    - COPD
    - Renal failure
    - Alcohol use
    - Certain drugs
  - Confirms a hepatic source of AP elevation
5’ Nucleotidase

- An enzyme found in
  - Liver
  - Intestine, brain, other tissues
- In liver, similar action to alkaline phosphatase
- Approximately equal value to AP
- Determine source of the liver injury
  - Hepatocellular vs cholestatic
Alkaline Phosphatase

- Enzyme
- Found in hepatocytes, bone osteoblasts and small intestine
- Commonly found in serum
- Can vary by age (higher in older), other factors
- When elevated, need to confirm hepatic cause
- ALT:AP ratios are suggestive:
  - < 2 is a hepatocellular pattern
  - 2 – 5 is a mixed pattern
  - > 5 is a cholestatic pattern
Liver Injury

**Cholestaticis**
- Bile unable to flow from the liver to the duodenum
  - Obstructive
  - Metabolic
- Intrahepatic
- Extrahepatic

**Hepatocellular**
- Aminotransferases present in high concentrations
- Injury to hepatocyte membrane causes leakage into the serum
- Acute vs chronic
Intrahepatic Causes of Cholestasis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Diagnostic Test(s)</th>
<th>Clinical Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary biliary cirrhosis</td>
<td>AMA</td>
<td>Middle-aged women (fatigue, pruritus)</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>MRCP or ERCP</td>
<td>Co-morbid ulcerative colitis</td>
</tr>
<tr>
<td>Infiltrative disorders (sarcoid, amyloidosis)</td>
<td>Imaging, biopsy</td>
<td>PMHx tuberculosis, sarcoid, malignancy</td>
</tr>
<tr>
<td>Drug induced liver injury (DILI)</td>
<td>Improvement after d/c</td>
<td>Medication history</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td>Relevant history</td>
</tr>
<tr>
<td>TPN</td>
<td></td>
<td>Relevant history</td>
</tr>
</tbody>
</table>
# Extrahepatic Causes of Cholestasis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Diagnostic Test(s)</th>
<th>Clinical Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choledolithiasis</td>
<td>Ultrasound, ERCP, MRCP</td>
<td>PMHx biliary colic, Acute onset RUQ pain, Fever, jaundice</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>ERCP</td>
<td>Comorbid ulcerative colitis</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Imaging CT or MRI</td>
<td>Presentation with jaundice and weight loss</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholagiocarcinoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Hepatic Causes of Acute LFT Elevation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Aminotransferase Levels</th>
<th>Diagnostic Tests</th>
<th>Clinical Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug- or toxin-induced (acetaminophen)</td>
<td>Can be &gt; 500</td>
<td>Acetaminophen level</td>
<td>History</td>
</tr>
<tr>
<td>Acute viral hepatitis</td>
<td>&gt; 500</td>
<td>Appropriate viral markers: HBV sAg IgM May not yet have Ab</td>
<td>Risk factor history</td>
</tr>
<tr>
<td>HAV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV (rare)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDV (HBV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parvovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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## Hepatic Causes of Acute LFT Elevation

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<thead>
<tr>
<th>Disease</th>
<th>Aminotransferase Levels</th>
<th>Diagnostic Tests</th>
<th>Clinical Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic hepatitis</td>
<td>Often &gt; 500 IU/l AST &gt; ALT</td>
<td></td>
<td>Recent hx hypotension</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>&lt; 400 IU/l AST : ALT &gt; 2:1</td>
<td></td>
<td>• PMHx excess EtOH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ↑↑t-bilirubin</td>
</tr>
<tr>
<td>Acute biliary obstruction</td>
<td>1000 IU/l ALT &gt; AST</td>
<td>Imaging</td>
<td>• Acute onset RUQ pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hx choledolithiasis</td>
</tr>
</tbody>
</table>
Hepatic Causes of Chronic LFT Elevation: Viral Infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Aminotransferase Levels</th>
<th>Diagnostic Tests</th>
<th>Clinical Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>&lt; 500 IU/l</td>
<td>HCV Ab</td>
<td>Risk factor(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCV RNA quant</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>ALT &gt; AST</td>
<td>HBVsAg</td>
<td>Risk factor(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV DNA</td>
<td></td>
</tr>
<tr>
<td>HDV (in HBV)</td>
<td></td>
<td>HDV Ab</td>
<td></td>
</tr>
</tbody>
</table>
# Hepatic Causes of Chronic LFT Elevation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Aminotransferase Levels</th>
<th>Diagnostic Tests</th>
<th>Clinical Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic liver disease</td>
<td>&lt; 400 IU/l</td>
<td></td>
<td>Relevant history</td>
</tr>
<tr>
<td></td>
<td>AST:ALT &gt;2:1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>&lt; 300 IU/l</td>
<td></td>
<td>• Comorbid metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>ALT&gt;AST</td>
<td></td>
<td>• Predisposition</td>
</tr>
<tr>
<td>Drug induced liver injury (DILI)</td>
<td>Up to 2000 IU/l</td>
<td>Improvement after d/c</td>
<td>Relevant history</td>
</tr>
<tr>
<td></td>
<td>ALT&gt;AST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Up to 2000 IU/l</td>
<td>ANA, ASMA, IgG levels</td>
<td>• Usually women</td>
</tr>
<tr>
<td></td>
<td>ALT&gt;AST</td>
<td></td>
<td>• Age 30 – 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Comorbid autoimmune disease</td>
</tr>
</tbody>
</table>
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<th>Disease</th>
<th>Aminotransferase Levels</th>
<th>Diagnostic Tests</th>
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<tbody>
<tr>
<td>Hereditary hemochromatosis</td>
<td>&lt;200 IU/l ALT&gt;AST</td>
<td>Ferritin</td>
<td>Family history</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iron saturation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IgG levels</td>
<td></td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Up to 2000 IU/l ALT&gt;AST</td>
<td>Ceruloplasmin 24h urine copper Slit lamp exam</td>
<td>Age &lt; 40 Low serum AP</td>
</tr>
<tr>
<td>α₁-antitrypsin deficiency</td>
<td>&lt;100 IU/l</td>
<td>α₁-antitrypsin level</td>
<td>Family hx Early onset lung disease</td>
</tr>
<tr>
<td>Infiltrative disease</td>
<td>&lt;500 IU/l ALT&gt;AST</td>
<td>Imaging</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>&lt;300 IU/l AST&gt;ALT</td>
<td>Biopsy</td>
<td>Platelets &lt; 150,000 Signs of portal hypertension</td>
</tr>
</tbody>
</table>
## Usual Patterns

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Amino-transferases</th>
<th>Alkaline Phosphatase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>
Hepatocellular Pattern: Work up

Acute $\leq 6$ months:
1. Review meds
2. Viral hepatitis serologies
3. Alcohol history
4. Tox screen (incl acetaminophen level)
5. ANA/aSMA
6. Ceruloplasmin (age $< 40$)

Chronic $> 6$ months:
1. Review meds
2. Viral hepatitis serologies
3. Alcohol history
4. Tox screen (with acet level)
5. ANA/aSMA
6. Ferritin, iron studies
7. Ceruloplasmin (age $< 40$)
8. Serum $\alpha^1$-antitrypsin level
9. ultrasound

Consider Biopsy:
Acute: if work up negative
Chronic: for staging
Cholestatic Pattern: Work up

↑AP

Isolated? Check GGT

Normal? Consider bone

Elevated?

Cholestatic pattern ↑↑AP ↑AST/ALT

Ultrasound of liver

Bile ducts not dilated

• Review med list
• Check AMA
• Consider biopsy

Bile ducts dilated

• Further imaging
• ERCP
Take a Careful History

- **Viral hepatitis (B and C)**
  - Up to 75% unaware of diagnosis
  - No acute event or symptoms in most cases
  - Long asymptomatic course
  - Are motivated by stigma not to disclose
  - May believe that a single remote event could not be problematic
  - Risk factors vs endemic areas
  - Unaware of family history
Take a Careful History

- Alcohol
  - Fear of repercussion/implications of disclosure
  - Family history can be a clue
  - Minimization is common
  - Quantities
Take a Careful History

- Drug induced liver injury
  - Concomitant use of meds
  - Acetaminophen overdose can be inadvertent
    - Recent viral illness?
    - Arthralgias
First Steps

- Is the elevation physiologic or transient?
- Alkaline phosphatase can be increased in
  - Pregnancy 3\textsuperscript{rd} trimester
  - Bone metabolism (post menopausal)
- Repeating the tests for confirmation is almost always indicated
Viral Hepatitis

- Risk factor based screening
  - Depends on history taking
  - Patient/provider relationship
  - Careful/thoughtful questioning
  - Once diagnosed, history may be less important

- Elevated liver enzymes is a risk factor for viral hepatitis

- Shared risk factors: usually makes sense to check them all.
Acute hepatitis A

- Foodborne
  - Ask about recent travel
  - Other potential food sources
- Check total Ab
- If positive or with higher suspicion, check IGM
- Rarely becomes chronic
- Consider vaccination if Ab- and ongoing risk
Hepatitis B

- Common in Asian, African, Caribbean populations
- Ask about family history of liver disease, cancer
- May have been exposed with either
  - No chronic infection
  - Inactive disease
- Check the following:
  - HBV cAb
  - HBV sAb
  - HBV sAg (if +, chronically infected)
- Consider vaccination
Hepatitis C

- Most common bloodborne disease worldwide (3%)\(^1\)
- Up to 75% unaware of their infection
- Risk factors vary
  - North America, Western Europe, etc: injected or nasal drug use (active or historical)
  - Worldwide: unsafe therapeutic injections
  - Highest rate: Egypt (~20%)
- Check HCV Ab, confirm + with HCV RNA(quant)
Alcoholic Liver Disease

- Concealing or minimizing alcohol (EtOH) use
- AST:ALT ratio ≥ 2:1\(^1\)
  - Relatively low serum activity of ALT in EtOH use
  - GGT is often also increased
- Usually chronic problem
- Characterized by relapse
- Requires counseling, referral

\(^1\)Cohen 1979
Drug-Induced Liver Injury

- Most common: acetaminophen
- Almost any drug can cause an elevation
- Supplements, herbs, homeopathic treatments
- Risk of acute liver failure
- Medications recently started
  - Risk benefit assessment
    - Hold medication and assess response
    - Continue close monitoring for essential medications
      - Consultation may be needed
## Drugs/Herbs Associated with DILI\(^1\)

### Drugs
- Acetaminophen
- Isoniazid
- Antibiotics
  - Penicillins
  - Ciprofloxacin
  - Nitrofurantoin
  - -azoles
  - Isoniazid
- Antiepileptics
  - Phenytoin
  - Carbamazepine
- Statins
- NSAIDs
- Sulfonylureas

### Herbs
- Chaparral
- Chinese herbs
- Gentian
- Germander
- Alchemilla
- Senna
- Shark cartilage
- Scutellaria

### Drugs of abuse
- Anabolic steroids
- Cocaine
- “Meth”
- “Angel dust”
- Glues/solvents
  - Toluene
  - chloroform

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\(^1\)Pratt 2000
Autoimmune Hepatitis

- Female : Male = 4:1
- Young to middle age
- Diagnostic criteria
  - Elevated aminotranferases
  - Absence of other causes
  - Presence of serologic characteristics
    - Polyclonal immunoglobulins (>2xULN)
    - Hypergammaglobulinemia (>80%)
    - ANA, ASMA, others (low sensitivity)
  - Confirmed with biopsy

¹Krawitt 1999, Manns 1984, Czaja 1988
Fatty Liver

- Non-alcoholic Fatty Liver Disease (NAFLD), Non-alcoholic Fatty Liver (NAFL), Hepatic Steatosis, Non-alcoholic Steatohepatitis (NASH)
- Increasing in incidence
- Projected to become leading transplant indication
- Elevated ALT/AST may be the only sign
  - Usually less than 4xULN
  - AST:ALT < 1:1 (vs EtOH)
- Confirm with ultrasound (or CT)
- Diagnosis of NASH requires biopsy (vs MRI)
- NASH is typically more progressive
- Weight loss is cornerstone of therapy
- Vitamin E, medical therapy are controversial
Hemochromatosis

- Iron overload
- Genetic disorder
- Screening labs:
  - Serum iron
  - Iron binding capacity
  - Serum ferritin
  - Transferrin saturation (Fe/TIBC) >45%
  - Genetic marker: HFE
- Confirmed with biopsy
  - Genetic marker +, LFT’s WNL, age <40 = no bx
Wilson’s Disease

- Biliary copper excretion disorder
- Genetic (no genetic test)
- My cause elevated ALT/AST
- Usual onset ages 5 – 25
- Consider up to age 40
- Labs:
  - Serum ceruloplasmin: reduced in ~85%
  - 24-hour quant urine: cu>100μg/24 hours
- Biopsy: >250μg cu/g
- Kaiser-Fleischer rings
\( \alpha_1 \)-Antitrypsin Deficiency

- Uncommon cause of LFT elevation
- Under-recognized
- Diagnosed by phenotyping
- Inherited disorder
- Involves lung, liver, sometimes skin
- Consider after all other causes have been ruled out
Celiac Sprue

- Small bowel disorder
- Causes inflammation
- Improves with removal of dietary gluten
- Elevated aminotransferases can be among a large number of findings
- Can be associated with primary biliary cirrhosis
Other Non-hepatic Causes

- Strenuous exercise
- Muscle:
  - Inherited disorders
  - Polymyositis
Still No Identified Cause?

- If <2xULN and no identified cause: monitor
- If persistently >2xULN: consider biopsy
  - Rarely lead to a diagnosis
  - Rarely change management
  - Can rule out causes/reassure
  - Risk/benefit analysis
Transient Elastography

- Measures liver stiffness
- Non-invasive
- Office procedure
- Score correlates with degree of fibrosis
- More sensitive at high and low ends

Source: www.echosens.com
42 yo male
HCV/EtOH cirrhosis

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2:15 PM</td>
<td>2:58 PM</td>
</tr>
<tr>
<td>ALBUMIN</td>
<td>3.5 - 4.9 G/DL</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>BILIRUBIN TOTAL</td>
<td>0.1 - 1.2 MG/DL</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>CALCIUM</td>
<td>8.5 - 10.5 MG/DL</td>
<td>8.3 (L)</td>
<td>8.7</td>
</tr>
<tr>
<td>CHLORIDE</td>
<td>96 - 108 MEQ/L</td>
<td>108</td>
<td>107</td>
</tr>
<tr>
<td>CREATININE</td>
<td>0.70 - 1.40 MG/DL</td>
<td>0.92</td>
<td>1.12</td>
</tr>
<tr>
<td>GLUCOSE</td>
<td>65 - 139 MG/DL</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>ALK. PHOSPHATASE</td>
<td>30 - 110 U/L</td>
<td>118 (H)</td>
<td>113 (H)</td>
</tr>
<tr>
<td>POTASSIUM</td>
<td>3.5 - 5.0 MEQ/L</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>PROTEIN TOTAL</td>
<td>6.0 - 8.3 G/DL</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>SODIUM</td>
<td>135 - 145 MEQ/L</td>
<td>139</td>
<td>140</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>1 - 50 U/L</td>
<td>60 (H)</td>
<td>80 (H)</td>
</tr>
<tr>
<td>UREA NITROGEN</td>
<td>11 - 25 MG/DL</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>CO2 TOTAL</td>
<td>22.0 - 32.0 MEQ/L</td>
<td>23.3</td>
<td>22.6</td>
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72 yo female
PBC/decompensated cirrhosis (EV)

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43 year old female, chronic HBV on treatment

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69 yo female chronic HCV, Remotely infected, Nonresponse x 1, currently on TW 3

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Thank you