Clinical Dilemmas in Liver Disease

Primary Care Update: 2013

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Outline
- What is the role of PCP in liver disease
- The common liver diseases in PC
- Approach to abnormal liver tests
- Nonalcoholic fatty liver disease
- Distinguishing cirrhosis vs no cirrhosis
- Management of cirrhosis in PC
- Medications and cirrhosis

Role of PCP in Liver Disease
- Screen, identify and diagnose liver dz
- Long term chronic disease management
- Manage co-morbidities simultaneously
- Monitor for disease progression
- Treat complications of cirrhosis
- Screen for HCC when appropriate

No disclosures
<table>
<thead>
<tr>
<th>Liver Diseases Common in Primary Care</th>
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<tbody>
<tr>
<td><strong>Alcoholic liver</strong></td>
</tr>
<tr>
<td>AST/ALT ratio often &gt;2:1; AST and ALT both &lt;500 IU/mL (if no other processes)</td>
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<tr>
<td><strong>Hepatitis C</strong></td>
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<tr>
<td>HCV Ab +, HCV RNA +, AST, ALT may be ↑ or normal</td>
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<tr>
<td><strong>Hepatitis B</strong></td>
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<tr>
<td>HBsAg +, HBV DNA +, HBsAg may be + or – AST, ALT ↑ or may be normal</td>
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<tr>
<td><strong>Hemochromatosis</strong></td>
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<tr>
<td>Ferritin elevated &gt;500, 45-55% iron saturation, HFE mutation positive</td>
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<tr>
<td><strong>NAFLD</strong></td>
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<tr>
<td>History of obesity, dyslipidemia, DM ↑ AST and/or ALT Fatty infiltration of liver on imaging</td>
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<tr>
<td><strong>Primary biliary cirrhosis</strong></td>
</tr>
<tr>
<td>pruritus, hyperpigmentation, hepatomegaly Women: elevated Alk Phos; Antibihomochondrial Ab</td>
</tr>
<tr>
<td><strong>Autoimmune hepatitis</strong></td>
</tr>
<tr>
<td>↑ AST and/or ALT; increased total IgG or gamma-globulin levels; serologic markers (ANA, SMA, anti-LKM-1, or anti-LC1)</td>
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### Abnormal LFTs

- 9% of general population had elevated ALT in NHANES study
- 25% of general population has elevated enzymes at some point
- Hepatocellular tests: AST, ALT
- Cholestatic tests: Alk phos, T Bili

### A Better ALT Upper Limit of Normal

- Updated upper limits
  - **Males**: 30 U/L (-25% from previous ULN)
  - **Females**: 19 U/L (-37% from previous ULN)
- Based on retrospective cohort study
  - 6835 first time blood donors 1995-1999
- ALT activity independently related to
  - BMI
- Abnormal lipid or carbohydrate metabolism

### Pattern 1: Elevated AST and/or ALT

- Medications, supplements
- Alcohol
- Non alcoholic fatty liver
- Hep B and C
- Hemochromatosis
- Muscle injury
- Thyroid
- Celiac
- Anorexia nervosa
- Autoimmune hepatitis
- Wilson’s disease
- Alpha 1 antitrypsin deficiency
Pattern 2: Elevated Bilirubin
- Fractionate the bilirubin
- If conjugated, get ultrasound
- If unconjugated, clinically appropriate further testing

<table>
<thead>
<tr>
<th>Unconjugated Bilirubin (indirect)</th>
<th>Conjugated Bilirubin (direct)</th>
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<tbody>
<tr>
<td>Gilbert's syndrome</td>
<td>Sepsis</td>
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<tr>
<td>Certain medications</td>
<td>TPN</td>
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<tr>
<td>Hemolysis</td>
<td>Choledochoolithasis</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Pancreatitis, Strictures</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Infiltrative diseases</td>
</tr>
</tbody>
</table>

Pattern 3: Isolated Alkaline Phosphatase
1. Order RUQ ultrasound first
   - Bile duct obstruction
2. Order AMA
   - Primary biliary cirrhosis (PBC)
3. Consider liver biopsy
   - Primary sclerosing cholangitis
   - Certain drugs such as androgenic steroids and phenytoin
   - Sarcoidosis, other granulomatous diseases

What is the most common liver disorder in the U.S?
1. Hepatitis C
2. Nonalcoholic fatty liver disease
3. Alcoholic liver disease
4. Hepatitis B

What does NAFLD look like?
- 56 yo male with BMI 35. Newly established care. Only known past history is hypertension. Takes no medications or herbs.
- A1C = 8.9, AST 65, ALT 54, LDL 176.
- Impression
  1) Obesity
  2) Diabetes Mellitus
  3) Hyperlipidemia
  4) Elevated transaminases
  5) Hypertension
NAFLD / NASH
Nonalcoholic steatohepatitis

- Hepatic fat (steatosis) in absence of significant alcohol consumption
- Typical features of fatty liver, obesity, type 2 diabetes mellitus, hyperlipidemia
  - Likelihood directly proportional to body weight
- Generally clinically stable, asymptomatic
  - Progression of fibrosis in 1/3 patients
  - Better prognosis than alcoholic hepatitis
- Liver enzymes elevated in 90%

Prevalence of NAFLD

- Most common liver disorder in Western industrialized countries
- Estimated prevalence of 20 – 40% percent of the general population.
- Among 400 US military personnel and their families (mean age 55), prevalence of NAFLD 46 %.
- Prevalence was increased in men, older individuals, and those with hypertension, obesity or diabetes.
- Hispanics and diabetics at greatest risk for NAFLD and NASH
- Presence of NAFLD associated with lifestyle factors including minimal exercise and fast food consumption

What is the difference between NAFLD and NASH?

- NASH is a subset of NAFLD
- Cannot distinguish NAFLD from NASH without histology
- NASH requires liver biopsy for diagnosis
- No imaging modality is able to differentiate between the benign or aggressive fatty liver
- In study of military personnel, NASH was confirmed by biopsy in 30 % of NAFLD patients.

Oral anti-diabetic agents in patients with NASH can:

1. Improve liver enzymes and liver damage and should be tried.
2. Worsen liver disease, cause lactic acidosis and should be avoided.
NASH Treatment – Safety of Agents

- Management of the associated conditions
- Many treatments for hyperlipidemia or diabetes may be underutilized
- Studies have examined rosiglitazone, pioglitazone, metformin, atorvastatin
  - Each of these shown to decrease aminotransferases and histology
  - RPCT pioglitazone + diet vs placebo + diet for DM + NASH. Pioglitazone group significant improvements in DM control, LFTs, hepatic fat with no adverse events

Determination of Cirrhosis

Clinical Presentation of Cirrhosis

- Approximately 40% are asymptomatic

Natural history of cirrhosis

- Compensated and decompensated cirrhosis are different entities
- Main outcome for compensated cirrhosis is decompensated cirrhosis
- Main outcome for decompensated cirrhosis is death
- HCC occurs along whole course of disease and worsens the outcome
Laboratory Clues of Cirrhosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AST, ALT</td>
<td>Moderately elevated, can be normal</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>Elevated up to 2-3 x normal</td>
</tr>
<tr>
<td>T Bili</td>
<td>Normal when compensated, then rises</td>
</tr>
<tr>
<td>INR</td>
<td>Increases as liver synthetic fxn decreases</td>
</tr>
<tr>
<td>Albumin</td>
<td>Decreases as synthetic fxn decreases</td>
</tr>
<tr>
<td></td>
<td>Can grade the severity of cirrhosis</td>
</tr>
<tr>
<td>Sodium</td>
<td>Hyponatremia common, severe in ESLD</td>
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<tr>
<td>WBC</td>
<td>Leukopenia, neutropenia</td>
</tr>
<tr>
<td>HCT</td>
<td>Acute and chronic anemia</td>
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<tr>
<td>Platelets</td>
<td>Thrombocytopenia</td>
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Utility of information from lab values

Which of the following lab tests would be most likely to accurately identify cirrhosis in a patient with chronic viral hepatitis?

1. Albumin 3.0
2. Platelet 95
3. ALT 229
4. Total bilirubin 1.5

How can we identify progression to cirrhosis before decompensation?

- Best predictors of cirrhosis in a patient with known liver disease:
  - Type II Diabetes
  - Platelet count

Fibrosis Staging: F0-4

- Cirrhosis can be ruled in by imaging but can’t be ruled out.
- Fibrosis stage cannot be determined on imaging or by LFTs.
- Fibrosis information clinically useful:
  - Prognosis - estimate risk for developing cirrhosis
  - Helps decision to delay or pursue treatment
  - Liver biopsy previously regarded as routine
  - Not required for HCV treatment consideration
  - Non-invasive fibrosis methods used off label
Non-Invasive Methods of Fibrosis Staging

- APRI score
  \[ APRI = \frac{AST \text{ elevation}}{\text{platelet}} \times 100 \]

Compensated cirrhosis

- Defined by absence of bleeding, ascites, encephalopathy and jaundice
- Median survival of 10-12 years until transition to decompensation
- Mostly asymptomatic

Decompensated cirrhosis

- Median survival of 2-4 years
- Ascites – 5 yr mortality 45%
- Variceal bleeding – 5 yr mortality 19%
- Ascites + bleeding – 5 yr mortality 56%

Management of Compensated Cirrhosis

- Calculate MELD every 4-6 months
- Visits every 4-6 months
- Refer for transplant evaluation when MELD is 8 or by local preferences
- No alcohol
- EGD every 2 years
- Ultrasound every 6-12 months for HCC screening
**Additional Management of Decompensated Cirrhosis**
- Calculate MELD every 4 months
- Visits every 4 months
- Manage uncomplicated ascites
- Manage uncomplicated acute variceal hemorrhage
- Diagnose and treat SBP
- Prevent recurrent SBP
- Hepatorenal treatment
- Encephalopathy treatment

**Immunizations for Chronic Liver Disease and Cirrhosis**
- Hepatitis A (if not immune)
- Hepatitis B (if not immune)
- Pneumococcal polysaccharide
- Seasonal Influenza
- Tdap
- Varicella zoster (if not immune)
- Herpes zoster vaccine (not age specific)

Cost effectiveness of pre-vaccination testing is controversial
Advisory Committee on Immunization Practices; Ann Intern Med 2012

**Immunize early in disease if possible**
- Efficacy may be better in earlier stage of disease, before decompensation
- Center for Medicare and Medicaid Services identified HAV and HBV vaccination as area for quality measurement
- HAV and HBV vaccination in HCV part of Medicare’s Physician Quality Reporting Initiative
- Vaccination rates in liver disease patients are only around 20%


**Weight Management**
- Obesity associated with steatosis
- Steatosis will typically increase rate of progression of fibrosis
- Primary care often major force on approaching weight and BMI
Alcohol and Tobacco

- Counseling patients on alcohol consumption
- Reducing alcohol intake for any patient with chronic liver disease
- Smoking risk factor for HCC in hepatitis B patients

Which of the following medications is not safe in patient with cirrhosis?

1. Acetaminophen
2. Ibuprofen
3. Lovastatin
4. Methadone
5. Gabapentin

Avoiding Hepatotoxic Drug Reactions

- Hepatotoxic reactions
  - transient LFT abnormalities to fulminant hepatic failure
  - Challenge is to distinguish safety and not undertreat
  - Vast number of drugs and conditions to consider

Examples of Acute Drug Liver Injury

<table>
<thead>
<tr>
<th>CHOLESTATIC PATTERN</th>
<th>HEPATITIS PATTERN</th>
</tr>
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<tbody>
<tr>
<td>Augmentin</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Iron sulfate</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>Phenytion</td>
</tr>
<tr>
<td>Bactrim</td>
<td>Methyldopa</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Diclofenac</td>
</tr>
<tr>
<td>Captopril</td>
<td></td>
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<tr>
<td>Estradiol</td>
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<tr>
<td></td>
<td>STEATOSIS PATTERN</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
</tr>
<tr>
<td>AZT, ddl, Stavudine</td>
<td></td>
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<tr>
<td>Valproic acid</td>
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</table>
Chronic Drug Liver Injury
- **HEPATITIS, Auto-immune like**
  - Nitrofurantoin, minocycline, statins, diclofenac
- **HEPATITIS, Viral like**
  - Phenytoin, dihydralazine
- **STEATOSIS**
  - Glucocorticoids, methotrexate, TPN, nifedipine, tamoxifen, valproate, amiodarone
- **FIBROSIS, CIRRHOSIS**
  - Almost any of above
  - Oral contraceptives, azathioprine, mercaptopurine

Statins and Cirrhosis
- Several recent retrospective and one large prospective trial suggest no significant risk of hepatotoxicity from statins
- Randomized placebo controlled trial with high dose pravastatin in pts with NASH or Hep C, the risk of elevated ALT was lower in pravastatin group than control group
- Beneficial effect on fatty liver

Metformin
- Concern for lactic acidosis
  - 110 cases of lactic acidosis, 12% had liver disease
- Abnormally high concentrations of metformin in the liver can increase lactate levels and precipitate lactic acidosis
- For safety, it is recommended to exclude patients who abuse alcohol and evidence of liver disease
- However, recent NASH studies support it’s use

Thiazolidinediones
- Troglitazone - over 100 cases of hepatotoxicity, withdrawn
  - Preexisting liver disease was not a risk factor
- Rosiglitazone, Pioglitazone
  - Do not appear have same hepatotoxic potential
- Recommendations from FDA
  - Baseline liver tests
  - Pretreatment ALT should be <2.5 x ULN
  - Test every 2 months for first year
  - Discontinue if remains >3 x ULN


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Pain Management in Cirrhosis

47 yo male with a history of alcohol dependency presents with 6 months of muscular low back pain. Physical exam: Gynecomastia. Platelets 90K, AST 70, ALT 52, T Bili 1.4, Albumin 3.1

Acetaminophen

- Misconception that acetaminophen should be strictly avoided
- Effective and safe if used at low doses and without alcohol use
- Recommended as side effect management for interferon treatment in viral hepatitis
- Maximum 2 grams/day.
- Chronic alcohol users are at risk of hepatotoxicity regardless of severity of liver disease

Potential Complications from NSAIDS in Liver Disease

- Higher risk of hepatotoxicity
- Renal toxicity, Hepatorenal
- Reduce renal plasma flow and GFR
- Diuretic-resistant ascites
  - Reduce the effect of diuretics, worsening ascites and edema
- Gastroesophageal ulceration
- Higher risk of variceal hemorrhage

COX-2 Inhibitors

- Limited data in cirrhotics
- Celecoxib
  - Low potential for liver injury
  - Less renal toxicity compared to naproxen and placebo in short-term but still reduced measures of renal function
**Opiates**

- **Fentanyl**
  - Appears safe, unchanged pharmacokinetics
- **Methadone**
  - Appears safe, unchanged pharmacokinetics
- **Morphine**
  - Reduced first pass hepatic metabolism
  - Use at reduced doses, shorter durations such as two-fold increase in dose interval
- **Oxycodone**
  - Peak plasma concentrations 50 percent greater in cirrhotics

**Recommendations for Pain**

- Remind all liver disease patients of the risks of NSAIDs, including ASA
- Avoid NSAIDs, ASA, COX-2 in cirrhosis
- For opioids, reduce the dose and lengthen the dose interval. Consider Fentanyl and Methadone for chronic use.
- Acetaminophen can be used up to 2 gm/day unless active alcohol use

**Prednisone and Liver Disease**

- 59 yo man with known chronic HCV and COPD presents with increased wheezing, coughing, SOB at rest. Already using Albuterol and Combivent.
- Physical exam with profound wheezing, and poor air movement and poor peak flow. Room air O2 sat is 89%.
- Can you give this patient oral prednisone given his HCV?

**Prednisone**

- Case reports raises HCV RNA viral titer
- Associated with worsening of chronic hepatitis B
- May worsen diabetes control for NASH patients
- Aspect of treatment for autoimmune hepatitis
- Controversial therapy for alcohol hepatitis
Herbal Supplements

- Complementary medicine is popular among patients with liver disease
- Relative paucity of clinical trials using herbs
- Many trials suggest that herbs can decrease transaminase levels
- Effects on long-term survival are conflicting or poorly studied

Use of Complementary Medicine

- Many patients do not mention herbal medicines when questioned
- Classified as diet and food supplements, not regulated by U.S. agencies
- 19% U.S. adults use natural products, 2002
- All physicians should ask patients about use of alternative medicines, herbs, vitamins

Popular Ideas on Liver Health

“Colon and Liver Cleansing-Detoxification

Cleanse the colon and the liver consecutively, focusing on the top two filtration organs.
First cleanse the colon with our 7-, 14- or 21-day Colon Cleanse, and follow up with a 7-day Liver Cleanse.

Then cleanse the colon again with a final 7-day Colon Cleanse.”
Some Herbals May Be Emerging Treatments of Liver Diseases

- Patients often use herbal therapies to treat their liver diseases
- Some products are being investigated for anti-fibrotic use
  - Milk thistle (silybum marianum)
  - Quercetin
  - Baicalin
  - Baicalein
  - Sho-saiko-to
  - Salvia miltiorrhiza (Dan-shen)

Some Herbs Known to be Hepatotoxic

- Pyrrolizidine alkaloids
- Chapparal leaf
- Jin Bu Huan
- Germander
- Mistletoe
- Skullcap
- Pennyroyal
- Kava
- Ma-huang
- Multiple herb products
- Prostata (saw palmetto)
- Greater celandine

Growing Evidence on Beneficial Effect of Coffee

- 3 or more cups of coffee per day associated with 53% lower risk of liver disease progression in HCV than for non-coffee drinkers.
- An effect was not observed for black or green tea.
- Coffee intake slows disease progression in patients with alcoholic cirrhosis and NAFLD
- Coffee intake is associated with a lower risk for nonalcoholic fatty liver disease NAFLD