Clinical Dilemmas in Liver Disease

Primary Care Update: 2012

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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

Liver Diseases Common in Primary Care

<table>
<thead>
<tr>
<th>Disease</th>
<th>Key Features</th>
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<tbody>
<tr>
<td>Alcoholic liver</td>
<td>AST/ALT ratio often &gt;2:1; AST and ALT both &lt;500 IU/mL (if no other processes)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>HCV Ab +, HCV RNA +, AST, ALT may be ↑ or normal</td>
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<tr>
<td>Hepatitis B</td>
<td>HBsAg +, HBV DNA +, HBeAg may be + or –, AST, ALT ↑ or may be normal</td>
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<tr>
<td>Hemochromatosis</td>
<td>Ferritin elevated &gt;500, 45-55% iron saturation, HFE mutation positive</td>
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<tr>
<td>NAFLD</td>
<td>History of obesity, dyslipidemia, DM, ↑ AST and/ALT, Fatty infiltration of liver on imaging</td>
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<tr>
<td>Primary biliary cirrhosis</td>
<td>pruritus, hyperpigmentation, hepatomegaly, Women; elevated Alk Phos, Antimitochondrial Ab</td>
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<tr>
<td>Autoimmune hepatitis</td>
<td>↑ AST and/ALT, increased total IgG or gamma-glutamyl 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

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>
</tr>
<tr>
<td>Certain medications</td>
<td>TPN</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Choledocholithiasis</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

AGA Guideline, Gastroenterology, 2002
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.

Approach to NASH Treatment

- Management of the associated conditions one of keys to treatment
- Many of the treatments for hyperlipidemia or diabetes may be underutilized
- Studies have examined rosiglitazone, pioglitazone, metformin, atorvastatin
  - Each of these shown to decrease aminotransferases and histology
- Observational studies had supported vitamin E

(Pioglitazone in DM and NASH

- Randomized placebo controlled trial
- Pioglitazone + diet vs. Placebo + diet
- Pioglitazone group:
  - Significantly improved glucose control, normalized LFTs, decreased hepatic fat, increased hepatic insulin sensitivity and improved histology
  - No adverse events

(Belfort, et al. NEJM, Nov 30, 2006)
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

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%

Manifestations of Cirrhosis are Variable
- Physical exam findings
  - Stigmata of chronic liver disease
- Incidental findings
  - Laboratory, radiology, during surgery
- Clinical decompensation
  - Ascites, variceal bleed, encephalopathy
- Many never come to clinical attention

Laboratory Clues of Cirrhosis

<table>
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<tr>
<th>Test</th>
<th>Description</th>
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<tbody>
<tr>
<td>AST, ALT</td>
<td>Moderately elevated, can be normal</td>
</tr>
<tr>
<td>Aik 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>Sodium</td>
<td>Hyponatremia common, severe in ESLD</td>
</tr>
<tr>
<td>WBC</td>
<td>Leukopenia, neutropenia</td>
</tr>
<tr>
<td>HCT</td>
<td>Acute and chronic anemia</td>
</tr>
<tr>
<td>Platelets</td>
<td>Thrombocytopenia</td>
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Radiographic Findings
- Often can suggest cirrhosis
- But not sensitive or specific enough for primary diagnostic tool
- May see small size, surface nodularity, increased echogenicity, irregular appearance
- Ultrasound, CT, MRI
**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

Medications and Cirrhosis

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

Subclinical Drug Liver Injury

ALT < 3x Upper Limit Normal
Benign
Asymptomatic
Resolve with drug discontinuation

- Antibiotics
- Lipid lowering drugs
- Sulfonylureas
- Salicylates
- Quinidine
- Isoniazid

Examples of Acute Drug Liver Injury

CHOLESTATIC PATTERN
- Augmentin
- Chlorpromazine
- Nafcillin
- Bactrim
- Rifampin
- Erythromycin
- Captopril
- Estradiol

HEPATITIS PATTERN
- Acetaminophen
- Iron sulfate
- Phenytoin
- Methyl dopa
- Isoniazid
- Diclofenac

STEATOSIS PATTERN
- Tetracycline
- AZT, ddl, Stavudine
- Valproic acid

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.

**Pain Management in Cirrhosis**
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

Opiods

- 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

Riley, Am J Gastro, 1998; Chitturi, Sem Liv Dis, 2002
**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

**Psychotropic Drugs**

- **Clozapine**
  - Increased aminotransferases
- **Risperidone**
  - Associated with hepatocellular injury
- **Clorpromazine, Haloperidal, Proclorperazine, Sulpiride**
  - Associated with cholestasis
- **Benzodiazipines**
  - Very low risk

**Antidepressants**

- **SSRIs, Bupropion, Venlafaxine, Trazadone, TCAs**
  - All hepatically metabolized but rare reports of liver injury
  - Abnormal LFTS in up to 0.5% fluoxetine but rare overt hepatotoxicity
  - Nefazadone – Associated with 25 cases of liver failure

**Mood Stabilizers**

- **Valproic Acid**
  - Used for mood stabilizer, migraines, epilepsy
  - Frequently not recommended if liver disease
    - Reversible increase in AST, ALT (1-10%)
    - Risk of liver injury 1 in 37,000 exposed
  - Associated with carnitine deficiency
  - May be safe for use if monitored
    - Among series of HCV patients taking VPA, ALT levels were unchanged compared to HCV patients taking other medications
**Anticonvulsants**
- Phenytoin
  - Acute hepatitis as part of reactive metabolic syndrome (RMS) – fever, rash, internal organ
  - 10-100 per 100,000 exposed
  - Includes LFT abnormalities in 50%
- Also associated with phenobarbital, carbamazepine, lamotrigine
- Topiramate – only one case of liver injury

**Tuberculosis Medications and Liver Disease**
- 27 yo Asian-American pharmacy student with chronic inactive hepatitis B, normal LFTs with low level HBV DNA titer.
- PPD tested before hospital rotation – positive test.
- What can you do?

**Isoniazid**
- Important medication with few alternatives
- Limited duration of use
- 50% of cases in first two months of use
- Threshold for discontinuing commonly set at aminotransferase level >= 5 times ULN, rather than 3 times limit.
- Monitor monthly during use
- If elevated, requires weekly monitoring

**Pyrazinamide/Rifampin**
- Higher incidence of liver test abnormalities than isoniazid
- Monitor more frequently
  - Baseline then week 1, 2, 4, 6, 8
- Because of importance and few alternatives, set threshold for discontinuation at >=5 times ULN
**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