NAFLD, NASH, and alcoholic liver disease
Jonathan Congeni MD

 Definitions
- NAFL (Fatty liver)
  - Hepatic steatosis when no other cause for fat accumulation are present (>5% fat without injury)
- NASH (20%)
  - Inflammation/fibrosis present (>5% fat with injury)
- NASH cirrhosis (10%)
  - End stage (stage IV) fibrosis present on liver biopsy

In the vast majority, NAFLD/NASH is assoc with metabolic comorbidities such as obesity, diabetes mellitus, and dyslipidemia (metabolic syndrome)
Why do we care?

- Patients with NAFLD, let alone NASH, have a significantly higher mortality rate than the general population.
- NAFL pretty benign, not the case with cirrhosis.
- Most common cause of death is CV disease.
- Third most common cause of HCC (EtOH, Hep C).
- Pure volume, not so much risk.
- Likely soon to be #1 reason for liver transplant.
Pathogenesis (a brief word)
- Unknown
- Insulin resistance seems to be key
- Two hit hypothesis, meaning a second “hit” or oxidative injury occurs to produce inflammation

Summary of Pathogenesis of NASH

Epidemiology
- Prevalence/Incidence
  - Most common liver disorder in the Western world
  - Incidence is increasing: 5.5% in the 80s, 9.8% in the 90s, 11% in the 2000s (based on abnormal LFTs w/o another exp)
  - In general population, prevalence ranges from 1.5-6.45%, much higher with metabolic syndrome (upwards of 80%)
- Demographics
  - Usually patients are diagnosed in their 40s-50s
  - Hispanics — Caucasians — African Americans
  - Gender/ethnic background/age all likely matter
Evaluation and clinical features

- Largely asymptomatic, often first coming to provider's attention with otherwise routine work up.
- Many come to attention after showing signs of decompensated cirrhosis.
- Ascites
- SBP
- Variceal hemorrhage
- Hepatocellular carcinoma (HCC)
- Non specific symptoms that have been attributed to the disease include fatigue, RUQ fullness/abdominal discomfort.
**Evaluation and Clinical features**

- Usually there will be a history of obesity, rapid weight changes, gestational diabetes, hyperlipidemia/triglyceridemia, or a family history of liver disease.
- Exclude other causes:
  - EtOH history
  - Herbs/Medication/Supplements
  - Systemic illness including celiac disease, IBD, endocrine history

**Labs**

- Typically have mild to moderate elevation in transaminase, though this can certainly vary.
- AST/ALT ratio usually < 1 (Helps to differentiate from EtOH).
- TB/Albumin usually WNL, particularly in early stages.
- If TB elevated, consider cirrhosis.
- Ferritin may be elevated, even as up to 1.5x ULN.
- Higher the ferritin, higher the chance of fibrosis.
- Degree of aminotransferase levels NOT indicative of disease severity.
- Rule out other causes:
  - Hemochromatosis, alcohol, AILD, viral hepatitis, DILI.

**Radiological findings**

- Often an incidental finding on thoracic/abdominal imaging for evaluating other symptoms or conditions similar to lab work-up.
- Need high index of suspicion.
- US “bright liver” – hyperechoic appearing liver (may be limited by body habitus).
- Look for nodular margin, “shrunken” liver to trigger evaluation for cirrhosis.
- Elastography – grades fibrosis well, limited role in steatosis evaluation.
- Good for monitoring disease, ruling out significant fibrosis.
- CT/MR - identifies steatosis, not sensitive to fibrosis or inflammation.
Biopsy?
- Difficult answer, no clear cut consensus to guide us
- Diagnosis is usually presumptive based on history, exam, labs, imaging (Process of elimination)
  - Pros
    - Only way to confirm/exclude NASH
    - NAFL generally pretty benign whereas NASH can progress to cirrhosis/liver failure
    - Suspect NAFL, diagnosis remains unclear
    - Motivation for lifestyle changes (fibrosis/inflammation present)
  - Cons
    - Expensive
    - Local expertise
    - Morbidity
    - Good prognosis
    - Lack of therapy

Consider checking a NAFLD fibrosis score
- Higher scores associated with increased mortality from cardiovascular disease
- Predicts advanced fibrosis taking into account 6 different variables
- Endorsed by AASLD
- Negative predictive value of 93%
- Positive predictive value of 90%
- Applying this model can avoid liver bx in 75% and is accurate in about 90%
- http://www.nafldscore.com/

Treatment
- Lifestyle modifications
  - Pharmacotherapy
Treatment

- Abstain from alcohol
- Vaccination
- Cardiovascular disease risk modification
  - HTN
  - HLD
  - DM

- Weight loss
  - Diet
    - The key to improvement in histopathological features of NASH
    - >10% weight loss associated with improvement in all features of NASH including portal inflammation and fibrosis
    - More significant weight loss, better chance at improvement
    - Compliance with a calorie-restricted diet over the long term is associated with sustained improvements in liver function and cardiovascular risk (Consider dietary/nutrition referral)
    - The specific macronutrient composition of the diet, over months to years, is less relevant than the end result of sustained weight loss
    - 1000-1200 kcal/day in women, 1200-1500 kcal/day in men

- Exercise
  - Large RCT assessing the effect of exercise on histopathology in NASH are lacking
  - Recent meta analysis noted improved HS, ALT unchanged
  - 30-60 minutes or more of moderate intensity aerobic physical activity of total 3 days/week seems beneficial for NASH
  - Most benefit seen with combination diet and exercise
  - Other benefits
    - Bariatric surgery
      - Improves long term survival and death from CVD and malignancy, but not non-cardiovascular causes of death in NASH
      - NASH resolution is common (60%), fibrosis improved as well
      - Risk, particularly with decompensated cirrhosis

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Treatment

Bariatric surgery
- Sustained weight loss hard to achieve, often harder to sustain
- 2/3 of morbidly obese undergoing gastric bypass have NAFL/NASH
- Improves or eliminates comorbid disease in most patients improving long term survival and death
- Role in those who have struggled to lose weight despite aggressive intervention


Treatment

Medications
- Options for pharmacologic, liver targeted therapy for NAFLD are limited and certainly not indicated for all patients
- Most therapy has reported on improvement in secondary outcomes, not ability to prevent advancement to cirrhosis
- Consider for those who do not achieve weight loss goals and have biopsy proven NASH

Vitamin E (Antioxidant) 800 U daily
- PIVENS trial
  - Non diabetic, non cirrhotic
  - Vitamin E improved both histology and transaminases
- Unclear long term effects
- AALSD, ACG, AGA joint 2012 guideline recommends Vitamin E at 800 U/day in those non diabetic pts with biopsy proven NASH
Treatment

- Pioglitazone
  - Improved liver histology in patients with and without T2DM and biopsy-proven NASH
  - Risk is weight gain, possible link to bladder CA
  - Cardiovascular risk still a bit unclear

- Ursodeoxycholic acid, omega 3 fatty acids, metformin
  - No backing with multiple studies conducted
  - Many of the studies claiming benefit were poorly powered or failed to show significant therapeutic benefit
  - Many new drugs/therapies currently being studied

Monitoring

- Serum aminotransferases every 6 months after instituting lifestyle modifications
- If no improvement despite goal weight loss, re-evaluate for alternative cause
- Consider viral/celiac/muscle disorder/lipid/HIV/rxbx/drug/alcohol
- NASH proven – Imaging every 3-4 years depending on weight loss success
- Great prognosis with no evidence of significant fibrosis
- NASH unproven or NAFLD – No routine imaging unless clinical status changes (significant weight gain/features of metabolic sx change/worsening LFTs)

Summary of PCP/NP work up

Abdominal US

Alcoholic Liver Disease

- Burden of alcoholic liver disease continues to grow
- Can range from steatosis to steatohepatitis to cirrhosis
- Steatosis can be seen within 2 weeks of regular consumption and resolves rapidly with abstinence
- Risk of advanced disease directly related to quantity of EtOH consumed
  - 1% for 30-40g daily, 6% for 120g daily
- Again important to distinguish between steatosis and steatohepatitis
  - Once steatohepatitis develops, risk of cirrhosis increases dramatically (14%)
- More likely to progress with ongoing alcohol consumption
Alcoholic hepatitis

- Acute onset of symptomatic hepatitis – majority will have a history of heavy alcohol consumption (>100g/day) for an extended period of time
- Incredibly high short term mortality (35% at one month with severe disease)

Epidemiology

- Usually between ages 40-50
- Typically daily alcohol abuse, sometimes around a stressful life event
- Alcohol consumption ceased just prior to or weeks before presentation

Clinical manifestations

Signs and symptoms

- Jaundice (usually within the last three months)
- Anorexia
- Fever (Be sure to rule out other sources of fever such as SBP)
- Tender hepatomegaly (RUQ pain)
- Malnurishment (Albumin and pre-albumin often down)

Labs

- Moderate elevation in transamizes, often in 2:1 AST/ALT ratio or more
- If transaminases higher than 500, consider other etiology (ischemia, infectious, drug)
- Elevated TB (mean 14-15), GGT, leukocytosis, thrombocytopenia, and INR

Diagnosis

- Clinical and laboratory features often adequate for diagnosis
- More complicated when a patient has underlying chronic liver disease, alcoholic cirrhosis, hepatitis B/C (Decompensated disease)
- In addition to CMP and CBC, need to check:
  - Check infectious hepatitis
  - Hepatitis A IGM
  - Hepatitis B surface antigen, antibody
  - Hepatitis B core IGM
  - Hepatitis C antibody
  - Abdominal US with doppler
Severity

- Discriminant function
  \[(4.6 \times \text{PT(unc)} - \text{control PT}) \times \text{serum TB}\]
  - DF > 32 needs pharmacotherapy (severe AHL), DF < 32 (mild to moderate)
- If you're considering treatment, likely need inpatient hospitalization with G/I/hepatology consult
  - Complications such as SBP/sepsis/AKI/sever coagulopathy/withdrawal all very common

Treatment

- Abstinence mainstay of treatment for both mild and severe disease
- Hydration and nutritional support as almost all patients have severe protein-calorie malnutrition
  - Goal is to provide adequate calories and protein, in addition to vitamin (thiamine, folate) and mineral (phosphate, magnesium)

- If treatment is indicated, there are two options:
  - Prednisolone 40mg daily x 28 days
  - Discontinue therapy with no response after 1 week (Lille score/TB/DF)
  - Contraindications (active infection)
  - Follow up considerations and adverse effects
  - Pentoxyfylline 400mg TID, discontinued with TB less than 5
  - Good secondary option when steroids contraindicated
  - Shown (though evidence is weak) to prevent renal failure
Questions

45 year old man admitted with nausea and jaundice. No history of fever.
Reports consuming a fifth of vodka a day for 15 years. Exam reveals tender hepatomegaly. TB is 6 mg/dl, albumin 3 gm/dl, AST 250 IU/L, ALT 110 IU/L, ALK 155 IU/L, INR 2.3, and creatinine 1.5 mg/dl. The most appropriate treatment for this patient is:

A: Rifaximin 400mg TID
B: Prednisolone 40 mg/day
C: Pentoxifylline 400 mg TID
D: Referral to a liver transplant center

Answer B

This patient has a discriminatory function of 43. Therefore, he meets the criteria for severe alcoholic hepatitis. Pentoxifylline is an option, but is considered second line unless there is a contraindication. Liver transplantation is generally not performed in patients with acute alcoholic hepatitis and a minimum of 6 months of abstinence is required by most transplant programs. The elevated creatinine and nausea suggest that the patient is dehydrated and maybe be nutritionally deficient. Could give vitamin K and monitor for response to treatment.

Questions

46 year old man is admitted to the hospital after being found unconscious by his family. He is known to consume more than a fifth of vodka a day for at least two decades. Physical exam reveals no fever. He has tender hepatomegaly and an albumin of 3 gm/dl. AST 1550 IU/L, ALT 1210 IU/L, ALK 155 IU/L, INR 2.8, creatinine 2.1 mg/dl. No leukocytosis. Next appropriate step for this patient is:

A: Doppler ultrasound of the liver
B: ERCP
C: Acetaminophen level
D: CPK level
E: Blood cultures
Answer C

Concern would be for acetaminophen toxicity. The isolated and very high AST and AST/ALT ratio is out of proportion to that seen in patients with alcoholic hepatocellular disease. ERCP is not indicated in the absence of localizing signs to suggest ascending cholangitis or biliary tract obstruction. Given the active alcohol abuse, liver transplantation is again not a good option. In the absence of features of autoimmune hepatitis, the transaminase elevation is much too high to blame on EtOH. Liver biopsy might help determine the degree of inflammation and fibrosis, though it will not change initial management. Treatment for acetaminophen ingestion could prove life saving.

Questions

A 40 y/o obese male (BMI >35) is found to have NASH. He has tried weight loss with multiple diets, dietitian support, and exercise but his liver enzymes remain elevated and he has only lost 5 lbs. Which of the following would you recommend?

A: Pioglitazone
B: Metformin
C: Bariatric surgery evaluation
D: Vitamin E

Answer C

Although Pioglitazone has been shown to improve insulin sensitivity, reduce hepatic steatosis, and mobilize visceral fat stores, weight gain during and after discontinuation of therapy is problematic. Metformin has not been shown to provide benefit in NASH. Vitamin E is an option, however, his young age and failed weight loss prompt referral for bariatric surgery evaluation.
Questions
A 62 y/o obese female presents in follow up with a history of HTN, GERD, and DM2 presents to establish care with complaints of ongoing fatigue and intermittent abdominal pain. Pain is described as primarily in the upper quadrants, worsened over the past 4 months. Difficult for her to identify any triggers, her establish care visit labs are notable for a TB of 1.3, ALT 56, AST 59, AIP 104. CBC is normal, including platelets. What is the best next step in work up?
A: GI referral
B: Re-check LFTs in 3 months
C: Abdominal US
D: Check an ANA, AMA, ASMA

Answer C
- GI referral may well be appropriate at some point in this patient's care, however, it is not the best first step. The patient has multiple risk factors for developing NAFLD. She doesn't have any labs to point to cirrhosis. If she did (thrombocytopenia/concerning exam or imaging findings), it would be reasonable. She has not been diagnosed with NAFLD nor has she made any lifestyle changes, so checking LFTs in 6 months without lifestyle counseling and work up, is premature. RUQ will not only help rule out advanced liver disease, it can further determine a cause and rule out other pathology (such as cholelithiasis/cholecystitis/choledocolithiasis) that could be contributing to her presentation. Obtain an extensive liver panel is premature as well with a likely diagnosis of NAFL and no prior lifestyle intervention attempted.

Questions
A 66 y/o male with a remote history of IVDU, history of HTN, GERD, and CAD returns to discuss his establish care blood work. He had not seen a doctor for many years. His BMP was normal. TB 1.6, ALT 57, AST 76, AIP 96, WBC 5.6, Hgb 11.8, platelets 137. He drinks alcohol daily, usually 2 beers each night, more when there is a "big" football game on TV. He maintains good compliance with his medications that were recently started and is interested in "catching up" on his health. What would be the best next step in evaluation of this patient?
A: Check a hepatitis A antibody, B surface antigen/antibody, C antibody
B: Check a RUQ US
C: Refer to GI
D: Discuss importance of screening colonoscopy
E: Provide alcohol abuse assessment and counseling
A primary care physician/NP has an incredibly difficult job. Knowing when to refer a patient to a specialist for assistance in dealing with a multitude of problems is difficult. This patient has multiple risk factors for chronic liver disease. He is thrombocytopenic and has markedly abnormal LFTs. He is at risk for alcohol-related chronic liver disease in addition to chronic hepatitis. A complete serologic liver work-up would be reasonable in addition to a liver biopsy if an etiology remains unclear. A referral would be appropriate. Prior to referral, checking a chronic hepatitis panel, RUQ US, and providing him with alcohol abuse counseling will likely prove beneficial to the accepting provider. He needs his preventative health care updated, which would include a screening colonoscopy as well.
Questions?