CURRENT AND FUTURE TREATMENT OPTIONS FOR PBC, NASH AND HEPATIC ENCEPHALOPATHY
Program Disclosure

- This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Purdue University College of Pharmacy and the Chronic Liver Disease Foundation. Purdue University School of Pharmacy is accredited by the ACCME to provide continuing medical education for physicians.

- This program is supported by educational grants from Intercept and Valeant.
Educational Objectives

• Review evidence-based management strategies for patients with PBC, NAFLD, NASH and HE

• Explain the risks and benefits of current and emerging treatments for patients with PBC, NAFLD, NASH and HE

• Identify barriers to the optimal management of patients with PBC, NAFLD, NASH and HE
Managing an Important Complication of Cirrhosis: Hepatic Encephalopathy
• 61 year old man with cirrhosis secondary to prior alcohol abuse
• Presented with alcoholic hepatitis with jaundice and ascites 18 months ago
• Alcohol abstinence since then (18 months)
• Episode of altered mental status 1 month ago; diagnosed as hepatic encephalopathy. Started on lactulose with directions for titration
• Ascites well controlled with diuretics (spironolactone 100 mg daily and furosemide 40 mg daily)
Case

- Patient was well until 1 day prior to presentation when he developed lethargy and slurred speech.
- Symptoms worsened until he became disoriented and his family brought him for evaluation.
- No fevers, GI bleeding, edema, increased abd girth or alcohol recidivism.
Examination revealed a chronically ill appearing man, oriented to name only

No evidence of head trauma; +asterixis noted on neuro exam

BP 104/62, HR 108, RR 20, SpO2 97%, T 37.1

Mucous membranes dry, no peripheral edema

Abdomen non-tender with palpable splenomegaly, firm nodular left lobe of liver in epigastrium; no fluid wave or distention

Labs: platelets 68,000, Bilirubin 1.3, AST 50, ALT 26, Alk Phos 180, INR 1.2, Na 129, BUN 44, creat of 1.8 (baseline 0.9); urine toxicology and BAL are negative

Any other diagnostics needed? What to do now?
Case

• Questions
  – What is/are the most likely diagnoses?
  – What are common provocations of acute overt HE?
  – Is serum NH3 level an important diagnostic strategy in a patient with this presentation?
  – How do you treat acute overt HE?
  – What is an appropriate strategy to prevent recurrence of HE?
Case

- Patient was hospitalized with overt HE and acute kidney injury, and hydrated with IV albumin and administered lactulose 2 tbsp tid
- Blood and urine cultures were obtained
- Diuretics were discontinued
- Mentation and electrolytes rapidly normalized
- Rifaximin 550 mg bid was added. Diuretics were not restarted but low sodium diet reinforced. The patient was discharged on lactulose and rifaximin
Causes of Chronic Liver Disease

- Chronic liver disease (CLD) is characterized as gradual destruction of liver tissue
  - In most cases, cirrhosis is the final stage
- HCV and Alcohol are the most common causes of cirrhosis in the US
- Cirrhosis due to HCV and NASH are growing in prevalence therefore cirrhosis rates are increasing

**Causes of Cirrhosis in the US**

- HBV 15%
- HCV 26%
- Alcohol 21%
- HCV plus Alcohol 15%
- Cryptogenic causes (Many cases actually are due to NAFLD) 18%
- Miscellaneous 5%

HBV = Hepatitis B; HCV = Hepatitis C; NASH = Nonalcoholic steatohepatitis; NAFLD = Nonalcoholic Fatty Liver Disease

Prevalence of Cirrhosis

• Experts estimate that 5.5 million people in the United States have cirrhosis
• Many patients with cirrhosis remain undiagnosed
  – 40% of cases of cirrhosis “latent”
• Twelfth leading cause of death in US

Compensated Cirrhosis May Be Difficult to Recognize

- Many patients present with normal liver enzymes
- Subtle clues may be overlooked
  - Thrombocytopenia
  - Muscle wasting
  - AST>ALT without alcohol consumption
- Risk factors may be subtle
  - Prior alcohol use
  - Remote drug use
  - Uncontrolled diabetes mellitus and obesity

Cirrhosis: Symptoms and Signs

- Anorexia, weight loss
- Weakness, fatigue
- Muscle loss, cramps
- Nausea
- Vague (RUQ) abdominal pain
- Pruritus
- Easy bruising, epistaxis
- GI bleeding
- Confusion, sleep disturbance
- Amenorrhea or irreg menses
- Spider angiomata
- Palmar erythema
- Gynecomastia, testicular atrophy
- Abdominal distention, edema
- Parotid hypertrophy
- Dupuytren’s contractures
- Clubbing, leukonychia
- Jaundice, icterus
- Caput medusa
- Splenomegaly
- Enlarged left or caudate lobe
- Asterixis, fetor hepaticus
- Cachexia

However…often asymptomatic
US Hospital Discharges Due to Cirrhosis Are Increasing

*ICD-9-CM diagnosis codes 571.2, 571.5, 571.6; all listed diagnoses.

Hospital Readmissions Among Patients with Decompensated Cirrhosis are Common

- Retrospective study of 402 patients from an academic transplant center
- Median follow-up: 203 days
- Included cirrhotic patients hospitalized for ascites, SBP, renal failure, HE, or variceal hemorrhage
- Median time to readmission: 67 days
- Median number of readmissions: 2 (range 0-40)
- Overall rate: 3 hospitalizations/person-year

Complications of Cirrhosis: Focus Will Be Hepatic Encephalopathy

Cirrhosis

- Portal hypertension
- Liver insufficiency

Encephalopathy

- “Coagulopathy”
- Jaundice
- Hypoalbuminemia

- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Variceal hemorrhage
- Ascites, Hydrothorax
- SBP
- Hepatorenal syndrome
HE Pathogenesis

- Toxins
- NH$_3$ Shunting
- GABA-BD receptors
- Failure to metabolize NH$_3$
- Bacterial action
- Protein load
Hepatic Encephalopathy: Pathophysiology

- Increased brain water, deterioration in neuropsychological function & hepatic encephalopathy
- Inflammation
- Cerebral Blood Flow
- Nitric Oxide & Oxidative Stress
- Proinflammatory Cytokines
- NH$_3$

Astrocyte Swelling

Glutamate & NH$_3$

Glutamine

Characterization of HE Stages

Categorization is often arbitrary and varies between raters

Worsening cognitive dysfunction

“Overt” HE Stages

Clinical Diagnosis

Clinical Classification of HE

Hepatic encephalopathy should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade</th>
<th>Covert</th>
<th>Time Course</th>
<th>Spontaneous or Precipitated</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>MHE</td>
<td></td>
<td>Episodic</td>
<td>Spontaneous</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td></td>
<td>Recurrent</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>Overt</td>
<td>Persistent</td>
<td>Precipitated (specify)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td></td>
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</tr>
</tbody>
</table>

• Hepatic encephalopathy should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).
Role of Ammonia Testing in HE

- “Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1)”

Specific Approach to Overt HE Treatment

• Four-pronged approach to management of HE (GRADE II-2, A, 1):
  – Initiation of care for patients with altered consciousness
  – Alternative causes of AMS should be sought and treated
    • e.g. diabetic ketoacidosis, drugs (benzodiazepines, neuroleptics, opioids), neuroinfections, electrolyte disorders, intracranial bleeding and stroke¹
  – Identification of precipitating factors and their correction
  – Commencement of empirical HE treatment

## FDA Approved Treatment Options for Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Potential Adverse Effects</th>
</tr>
</thead>
</table>
| **Lactulose** | • Decreases blood ammonia concentration  
- Promotes elimination of $\text{NH}_3$  
- Fermentation by bacteria acidify colon and prevent absorption  
- Reduces urease-producing bacteria | Overuse can lead to aspiration, dehydration, hypernatremia, and severe perianal skin irritation; overuse can even precipitate HE$^2$ |
| **Rifaximin** | • Decreases blood ammonia concentration  
- Broad spectrum antibiotic; results in a change in bowel flora  
- May cause downregulation of intestinal glutaminase activity | Diarrhea (due to overgrowth of $C$ diff) peripheral edema, nausea, dizziness, fatigue, and ascites$^3$ |
| **Neomycin** | • Decreases blood ammonia concentration  
- Inhibits intestinal glutaminase. Use limited.  
- Not recommended for chronic use | Risk of ototoxicity and nephrotoxicity with long-term treatment due to some systemic absorption$^4$ |

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172 Cirrhotic Patients Screened

120 Patients Enrolled

Randomization

Lactulose (30-60 mL TID) + Rifaximin (one 400 mg capsule TID)  
\( n=63 \) (10 grade 2, 20 grade 3, 33 grade 4)

Lactulose (30-60 mL TID) + Placebo (one sugar capsule TID)  
\( n=57 \) (12 grade 2, 20 grade 3, 25 grade 4)

Treatment Approach for Episodic OHE: Lactulose + Rifaximin vs. Lactulose

- Reversal of HE
  - Lactulose + Rifaximin: 76% (48/63)
  - Lactulose + Placebo: 44% (25/57)
  - P-value: p=0.004

- Death
  - Lactulose + Rifaximin: 24% (15/63)
  - Lactulose + Placebo: 49% (28/57)
  - P-value: p=<0.05

• Given via NG tube until recovery from HE or a maximum of 10 days
• Hospital stay shorter with Lac+ Rfx than Lac+ Pbo (5.8±3.4 vs. 8.2±4.6 days, p=0.001)

Prevention of Overt HE (OHE)

- Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1)
- Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1)
- Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE (GRADE III, B, 1)
- Under circumstances where the precipitating factors have been well controlled (i.e., infections and VB) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2)
Secondary Prophylactic Therapy
Randomized, Placebo-Controlled Phase 3 Study of Rifaximin in 229 Patients

- Study evaluated the efficacy and safety of rifaximin (with lactulose) for maintaining remission of HE episodes in outpatients with a history of recurrent OHE
- Primary efficacy end point: time to first breakthrough episode of HE
- Key secondary end point: time to the first hospitalization involving HE
- Eligibility criteria:
  - Age ≥18 years, Cirrhosis
  - ≥2 episodes OHE (Conn score ≥2) during the previous 6 months
  - Remission (Conn score, 0 or 1) at enrollment
  - MELD score ≤25

Secondary Prophylaxis of OHE: Rifaximin vs. Placebo

Randomization and Follow-up

Rifaximin 550 mg BID for 6 mo (n=140)

- Discontinued n=52 (37%)
  - Breakthrough HE: n=28
  - Adverse event: n=8
  - Death: n=6
  - Patient request: n=6
  - Exclusion criteria: n=1
  - Other: n=3

- Completed Study n=88

Placebo for 6 mo (n=159)

- Discontinued n=93 (58%)
  - Breakthrough HE: n=69
  - Patient request: n=9
  - Adverse event: n=7
  - Death: n=3
  - Exclusion criteria: n=3
  - Other: n=2

- Completed Study n=66

~91% of patients in both arms were on lactulose at baseline and during the study

Rifaximin Treatment in OHE: Time to First Breakthrough Episode (Primary End Point)

Hazard ratio with rifaximin, 0.42 (95% CI, 0.28-0.64) 

$p < .001$

Rifaximin Treatment in OHE: Time to First HE-Related Hospitalization (Secondary Endpoint)

Hazard ratio with rifaximin, 0.50 (95% CI, 0.29-0.87)  
\( p = 0.01 \)

Conclusions

• Hepatic encephalopathy is a major complication of cirrhosis
• HE is treatable and active interventions can reduce recurrence risks and decrease hospital admission rates
• Lactulose is indicated for acute HE treatment; Rifaximin is indicated for prophylaxis of HE recurrence
• Familiarize yourself with new guidelines for its diagnosis, classification, and treatment
PBC: Primary Biliary Cirrhosis is now Primary Biliary Cholangitis
Case 1

- 65 year old woman
- Abnormal liver enzymes during annual physical: Alk Phos 368, AST 51, ALT 60, Tbili 1.1
- Notes mild fatigue
- AMA + at 1:640, liver biopsy shows stage I PBC
- Started on ursodeoxycholic acid at 13-15mg/kg/day (UDCA)
- 12 months later her liver tests are normal 😊
• The “traditional” view of PBC
  – Mild disease in an elderly woman
  – Mild fatigue or pruritus at presentation
  – Responds well to UDCA
  – Risk very low and unlikely to die of liver disease or need transplant
Case 2

- 37 year old woman
- Profound fatigue,
- Alk Phos 630, ALT 122, T.Bili 1.6, AMA+(1:320)
- Liver biopsy consistent with stage 2 PBC but also with marked interface hepatitis
- Started UDCA at 15mg/kg/d
- 6 months later: Alk Phos 488, ALT 587, T.Bili 4.7, severely fatigued
- What do you think is going on?
Case 2

- PBC with Autoimmune Hepatitis Overlap Syndrome
  - Aggressive disease in a young woman or man
  - Fatigue as a prominent or even life altering feature
  - Minimal response to UDCA (and no symptom improvement)
  - Sp100/Gp210 ANA and interface hepatitis
  - High risk of need for transplant or death
  - Needs second line therapy beyond UDCA
What is PBC?

- Name changed to “Primary Biliary Cholangitis” in 2015
- Chronic cholestatic disease with a progressive course extending over decades; rate of progression varies greatly
- 95% of PBC patients are women
- Potential indication for liver transplantation: 394 of 15,044 (2.6%) waitlisted candidates in U.S.¹
- Often asymptomatic in early disease
- AMA+ in 90-95%, Quantitative IgM levels often elevated
- Extrahepatic associations: fatigue, pruritus, Sicca syndrome, hyperlipidemia, osteoporosis, celiac disease, RA, and scleroderma

¹ optn.transplant.hrsa.gov accessed 8/16/2016
Natural History of PBC varies

Diagram showing the progression of PBC with age, indicating clinical jaundice, symptomatic jaundice, asymptomatic jaundice, hepatic failure, varices, itching, anti-gp210, anti-centromere, slow progression type, portal hypertension type, jaundice/hepatic failure type, and death.
Causes and Markers of PBC

- Autoimmune disease thought to be due to a combination of genetic predisposition and environmental triggers
- High degree of specificity for involvement of the small intrahepatic bile ducts
- Serologic hallmark of PBC is the AMA, a highly disease-specific autoantibody found in 90-95% of patients and less than 1% of controls.
AASLD Suggested Diagnostic Algorithm for Patients With Suspected PBC

1. Elevated serum alkaline phosphatase (ALP) activity
2. Exclude other causes of liver disease including alcohol and drugs; consider bone disease, pregnancy
3. Cross sectional imaging of liver to exclude biliary obstruction
4. AMA (Antimitochondrial antibody), ANA (antinuclear antibody), ASMA (anti-smooth muscle antibody)
5. Consider liver biopsy, especially if AST>5x ULN or AMA -

Ursodeoxycholic Acid (UDCA)

- Orally administered, naturally occurring, lipophilic secondary bile acid
- UDCA 13-15 mg/kg/day was the only FDA approved therapy for PBC until 5/2016
- Improvement in liver tests may be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months
- However, up to 40% of PBC patients treated with UDCA have a suboptimal response (optimal response is ALP < 1.67 x ULN)

ALP = alkaline phosphatase
Obeticholic Acid (OCA): A Modified Bile Acid and FXR Agonist

OCA is a bile acid analogue that selectively activates the nuclear hormone receptor farnesoid X receptor (FXR), causing the effects listed below.

OCA in Patients with PBC: POISE Study Design

Randomization Strata
Subjects stratified 1:1:1 by:
1) ALP >3x ULN and/or AST >2x ULN and/or total bilirubin >ULN (Paris I)
2) Not receiving UDCA treatment

- OCA Titration at 6 Months: Subjects in OCA titration arm titrated from 5 mg to 10 mg at Month 6 if they met any of the following criteria at the Month 6 assessment:
  1. The primary endpoint (ALP <1.67x ULN or bilirubin ≤ULN) was not achieved
  2. No evidence of tolerability issues, e.g. pruritus

Nevens F et al. . A Phase 3, Double Blind, Placebo Controlled Trial Of Obeticholic Acid In Patients With Primary Biliary Cirrhosis (POISE) Presented at: American Association for the Study of Liver Diseases Annual Meeting 2014; November 7-11, 2014; Boston, MA.
Primary Objective and Patient Population

- To assess the proportion of patients achieving ALP <1.67 x ULN and a decrease of ≥15% and total bilirubin ≤ULN

**Inclusion**
- PBC diagnosis (EASL and AASLD guidelines)
- ALP ≥1.67 x ULN and/or total bilirubin >ULN to <2 x ULN
- Stable UDCA or unable to tolerate UDCA

**Exclusion**
- Concomitant liver diseases, decompensation, severe pruritus requiring treatment

**Randomization Strata**
- UDCA (yes/no)
- Paris I

**Percent Achieving Primary Endpoint**

Response:
ALP <1.67x ULN with bilirubin ≤ULN and ≥15% reduction in ALP

P values obtained using Cochran-Mantel-Haenszel stratified by randomization strata factor.

**Titration OCA group:** 5 mg OCA for 6 months ->10 mg OCA if well tolerated & ALP >1.67x ULN or bilirubin >ULN

Nevens F et al. A Phase 3, Double Blind, Placebo Controlled Trial Of Obeticholic Acid In Patients With Primary Biliary Cirrhosis (POISE) Presented at: American Association for the Study of Liver Diseases Annual Meeting 2014; November 7-11, 2014; Boston, MA.
OCA Treatment Significantly Reduced ALP

**Titration OCA** group: 5 mg OCA for 6 months then titrated to 10 mg OCA if tolerated & ALP ≥1.67x ULN or bilirubin >ULN

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***p<0.0001 vs. placebo for all post baseline values of Titration OCA and 10 mg OCA groups

Baseline values (mean ± SE, U/L): Placebo 327 ± 13; Titrated OCA: 326 ± 14; 10 mg OCA: 316 ± 12; n=216
OCA Treatment Resulted in Significant Decreases in Markers of Hepatobiliary Damage

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**Titration OCA group:** 5 mg OCA for 6 months then titrated to 10 mg OCA if tolerated & ALP ≥1.67x ULN or bilirubin >ULN

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OCA Treatment Stabilized Bilirubin Over Time

Placebo (n=73)  Titration OCA (n=70)  10 mg OCA (n=73)

Total Bilirubin

Direct Bilirubin

Note: Bilirubin 1mg/dL = 17 micromol/L (normal = 5.13 – 17.1 micromol/L)

*p<0.05 vs. placebo
Baseline Direct Bilirubin (mean ± SE, µmol/L): Placebo 5.5 ± 0.7; Titration OCA: 4.5 ± 0.5; 10 mg OCA: 4.9 ± 0.5
Baseline Total Bilirubin (mean ± SE, µmol/L): Placebo 11.8 ± 0.9; Titration OCA: 10.3 ± 0.7; 10 mg OCA: 11.3 ± 0.8

Titration OCA group: 5 mg OCA for 6 months then titrated to 10 mg OCA if tolerated & ALP ≥1.67x ULN or bilirubin >ULN

Nevens F et al. A Phase 3, Double Blind, Placebo Controlled Trial Of Obeticholic Acid In Patients With Primary Biliary Cirrhosis (POISE) Presented at: American Association for the Study of Liver Diseases Annual Meeting 2014; November 7-11, 2014; Boston, MA.
## Adverse Events in OCA Phase 3 Study (POISE)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=73)</th>
<th>Titrated OCA (n=70)</th>
<th>10 mg OCA (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>D/C due to pruritus, n (%)</strong></td>
<td>0</td>
<td>1 (1%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td><strong>TEAEs without pruritus, n (%)</strong></td>
<td>66 (90%)</td>
<td>62 (89%)</td>
<td>63 (86%)</td>
</tr>
<tr>
<td><strong>TEAE pruritus, n (%)</strong></td>
<td>28 (38%)</td>
<td>39 (56%)</td>
<td>50 (68%)</td>
</tr>
<tr>
<td><strong>SAEs, n (%)</strong></td>
<td>3 (4%)</td>
<td>11 (16%)</td>
<td>8 (11%)</td>
</tr>
</tbody>
</table>

Abbreviations: D/C, discontinuation; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cirrhosis; SAE, serious adverse event; TEAE, treatment-emergent adverse effect
Overall Findings

• The effect of OCA was consistent independent of age at diagnosis, duration of PBC and baseline ALP.

• Titration from 5 to 10 mg based on clinical response improved tolerance, minimized dropouts due to pruritus, and showed comparable efficacy to 10 mg OCA after 1 year. Thus, starting patients on OCA 5 mg with titration to 10 mg based on the clinical response appears to be an appropriate dosing strategy.

• OCA given to individuals with PBC with an inadequate response to or unable to tolerate UDCA produced a significant clinically meaningful improvement in liver biochemistry, which has been shown to correlate strongly with clinical benefit.
Long-term Management of Patients with PBC (AASLD Guidance)

- Liver tests every 3-6 months
- Thyroid status (TSH) annually
- Bone mineral densitometry every 2-4 years
- Vitamins A, D, K annually if bilirubin >2.0
- Upper endoscopy every 1-3 years if cirrhotic or Mayo risk score >4.1
- Ultrasound ± AFP every 6 months in patients with known or suspected cirrhosis

Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)
Case Presentation

- 64 year old female who presents for persistent elevation of aminotransferases
- Fatigue and arthritis in her knees; often sleepy when she wakes
- Meds: lisinopril, simvastatin, metformin, H2-blockers, multivitamin, ‘Liv52’ supplement
- Past medical history: Diabetes, hypertension, hypercholesterolemia, GERD, arthritis
- Family history: No liver disease, liver cancer or cirrhosis. Mother and sister have diabetes. Mother had a heart attack at age 66.
- Physical exam is unremarkable, except for obesity and acanthosis nigricans
- Blood pressure: 139/84, BMI: 32 kg/m², Waist circumference: 44 inches
Case Presentation

- CBC normal except for platelets: 126,000
- Albumin (3.6 - 5.1 g/dL): 4.3 (repeat 4.1)
- Bilirubin, Total (0.2 - 1.2 mg/dL): 0.6 (repeat 0.9)
- AST (10 - 40 U/L): 65 (repeat 120)
- ALT (9 - 46 U/L): 75 (repeat 112)
- Alk Phos (40 - 115 U/L): 91 (repeat 93)
- HCV Ab & HBs Ag: Negative
- ASMA, AMA, ANA: Negative
- Iron saturation: 28%
- Ferritin: 446
- Alpha 1 antitrypsin: 249
- Abdominal ultrasound – Increased liver echotexture suggestive of fatty liver
- Fibroscan – Inconclusive (technically limited due to increased body habitus)

What should we do next?
Case Presentation: Liver Biopsy Results

• Microscopic description
  – 17 mm specimen containing more than 11 portal tracts
  – Steatosis with scattered lobular and portal inflammation and prominent hepatocellular ballooning with a number of Mallory bodies, indicating an active steatohepatitis
  – Trichrome stain shows extensive pericellular fibrosis as well as several areas of bridging fibrosis

• Diagnosis
  – Steatohepatitis, nonalcoholic by history, with bridging fibrosis (stage 3)

What does this mean and what should we do next?
Adult Obesity in America 2014

Percent of Obese Adults (Body Mass Index of 30+)

- 20 - 24.9%
- 25 - 29.9%
- 30-34.9%
- 35%+

Adult Obesity in America 2011-12

- Obese: 34.9%
- Overweight or Obese: 68.5%

Childhood Obesity in America 2011-12

- Obese: 16.9%
- Overweight or Obese: 31.8%

http://stateofobesity.org/adult-obesity/
Diseases Associated with Visceral Obesity

NAFLD is Closely Associated with Visceral Obesity and Insulin Resistance

- Visceral Obesity
  - Dyslipidemia
  - Hypertension
  - Endothelial Dysfunction
  - Atherosclerosis
  - Insulin Resistance
  - Type 2 Diabetes
  - Coronary Artery Disease (CAD)
  - Non-alcoholic Fatty Liver Disease (NAFLD)
  - Polycystic Ovarian Syndrome (PCOS)
The Spectrum of NAFLD

Normal

Simple Steatosis or “NAFL”

NASH

• Exclusion of liver diseases (HCV & ETOH)
• Requires specific pathologic criteria for NASH
• Important for prognosis

Natural History of NAFLD

NAFLD

- ~70-75% Isolated Fatty Liver
  - ~7.2% over 6.5 years
  - Possible sampling variability with some risk of progression

- ~20-25% Fatty Liver with Mild Inflammation
  - ~11% over 15 years, but significant variability
  - Possible sampling variability with some risk of progression

NASH

- Cardiovascular
- Malignancy
- Liver-related
- NASH with fibrosis portends worse prognosis
  - Fibrosis progression a/w DM, severe IR, weight gain >5kg, rising ALT, AST

NASH Cirrhosis

- 19-45% over 7-10 years

HCC

- ~11% over 15 years, but significant variability

Decompensation

1. ↑ risk of death compared with general population
   1. Cardiovascular
   2. Malignancy
   3. Liver-related
2. NASH with fibrosis portends worse prognosis
   1. Fibrosis progression a/w DM, severe IR, weight gain >5kg, rising ALT, AST

What Are the Clinical Predictors of Advanced Fibrosis In NAFLD?

- NAFLD with liver biopsy (N=432)
- In multivariate analysis, elevated AST and ALT, presence of diabetes mellitus, male gender and Caucasian ethnicity were associated with moderate to severe fibrosis (p<0.0001)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Advanced Fibrosis OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.61 (1.21-2.01)</td>
<td>0.0374</td>
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<tr>
<td>Diabetes</td>
<td>1.64 (1.13-2.17)</td>
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<tr>
<td>HTN and DM</td>
<td>1.69 (1.11-2.28)</td>
<td>0.0246</td>
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<tr>
<td>HTN+DM+VO</td>
<td>1.72 (1.13-2.31)</td>
<td>0.0205</td>
</tr>
</tbody>
</table>

Red Flags for NASH

- Age
- Gender
- Hispanic
- Hypertension
- Obesity
- Diabetes
- ALT and AST level
- AST/ALT ratio
- Insulin level
- Genetic variation of PNPLA3

No lab test or imaging study will be able to predict with 100% accuracy.

The more risk factors... the more concern.
The NAFLD fibrosis score (NFS) is a panel comprising six variables of:
- Age
- Hyperglycemia
- BMI
- Platelet count
- Albumin
- AST/ALT ratio

NAFLD fibrosis score:
- >0.676; advanced fibrosis diagnosed with high accuracy (PPV 82-90%)
- < -1.455; advanced fibrosis excluded with high accuracy (NPV 88-93%)
- Between -1.455 and 0.676; diagnosis “indeterminate”

AUROC 0.84

NAFLD Guideline Recommendations

Non-invasive Assessment

- NAFLD Fibrosis Score is a clinically useful tool for identifying NAFLD patients with higher likelihood of having bridging fibrosis and/or cirrhosis (Strength - 1, Evidence - B)

- Although serum/plasma CK18 is a promising biomarker for identifying steatohepatitis, it is premature to recommend in routine clinical practice (Strength - 1, Evidence - B)

NAFLD Guideline Recommendations

Role of Biopsy

• Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis (Strength - 1, Evidence - B)

• Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy (Strength - 1, Evidence - B)

Goals of Liver Biopsy

• Identify NASH (steatosis, ballooning, inflammation)
  – Establish diagnosis
  – Clinical trials

• Staging of disease (fibrosis)

• Rule out concomitant liver disease (iron overload, autoimmune hepatitis, etc)

• Prognosis
Transient Elastography

- Allows painless and simultaneous measurement of two quantitative parameters:
  - Liver stiffness expressed in kPa
    - Correlated to liver fibrosis¹
  - Controlled Attenuation Parameter (CAP™) expressed in dB/meter
    - Correlated to liver steatosis²
- Both quantitative parameters are assessed on the same volume of liver tissue
- 100 times bigger than liver biopsy

Transient Elastography

- Measures velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver
  - Normal liver: ~5.5 kPa
- Good performance for excluding advanced stage disease (stage 3-4)
- User-friendly, short procedure time
- Problems still with severe obesity, ascites, operator experience
- False positives: acute hepatitis, extrahepatic cholestasis and congestion
- XL probe has ~25% unreliable results; cut-off concerns
- **Not very good in our hands at predicting fibrosis in NAFLD patients**

Treatment and Intervention
# Treatment of NAFLD Regimens

## Regimens Used to Treat NAFLD/NASH

- Life style modification and weight loss
- Weight loss medications
- Lipid Lowering agents (statins, fibrates)
- Anti-obesity medications
- Antioxidants
  - Vitamin E
  - Vitamin C
  - Betaine
  - N-Acetyl-cysteine
  - Lecithin
  - Silymarin
  - Beta-carotene
  - EPA
- Treatment of IR
- PPAR agonists
- Anti-TNF agents (pentoxifylline)
- ACE inhibitors/ARBs
- Caspase inhibitors
- Bile Acid-Ursodeoxycholic acid (UDCA)
- Probiotics

## AASLD, ACG, AGA NAFLD Guideline

### Weight loss and Life Style Modification

- Weight loss reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity (Strength –1, Evidence- A)
  - Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation (Strength – 1, Evidence - B)
- Exercise alone in NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown (Strength – 1, Evidence - B)

### Medical Regimens

- Vitamin E 800 IU/day improves liver histology in non-diabetics with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population. (Strength -1, Quality - B)

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farnesoid X Receptor (FXR) Agonist</td>
<td>Obeticholic Acid (OCA)</td>
</tr>
<tr>
<td>Anti-lysyl oxidase-like 2 monoclonal antibody</td>
<td>Simtuzumab</td>
</tr>
<tr>
<td>Fatty acid/bile acid conjugate</td>
<td>Aramchol</td>
</tr>
<tr>
<td>Dual inhibitor of CCR2 and CCR5</td>
<td>Cenicriviroc</td>
</tr>
<tr>
<td>Dual peroxisome proliferator-activated receptor alpha/delta agonist</td>
<td>GFT505</td>
</tr>
<tr>
<td>Probiotics</td>
<td>VSL#3</td>
</tr>
</tbody>
</table>
The PIVENS Trial

- Large RCT in 247 non-diabetic patients with NASH
- Randomized to Pioglitazone (30mg/day), Vitamin E (800 IU/day), or Pbo for 24 months
- Primary endpoint: 2 point improvement in NAFLD Activity Score (NAS) with
  - At least 1 point improvement in ballooning AND 1-point improvement in either lobular inflammation or steatosis
  - No worsening of fibrosis
  - p = 0.025 for significance
- Vitamin E, as compared with placebo, was associated with a significantly higher rate of improvement in NASH (43% vs. 19%, p=0.001)
- Pioglitazone, as compared with placebo, was NOT associated with a significantly higher rate of improvement in NASH (34% and 19%, respectively; p=0.04)
- AST and ALT improved with Vitamin E and Pioglitazone, compared with placebo (p<0.001 for both comparisons)
- Both agents demonstrated reductions in steatosis (p=0.005 for Vitamin E and P<0.001 for Pioglitazone) and lobular inflammation (p=0.02 for Vitamin E and P=0.004 for Pioglitazone) but not with improvement in fibrosis (p=0.24 for Vitamin E and P=0.12 for Pioglitazone).

\[
\text{NAS (0-8) = Ballooning (0-2) + Lobular Inflammation (0-3) + Steatosis (0-3)}
\]

**FLINT Trial Design-Obeticholic Acid (OCA)**

- **Primary endpoint:** liver histological improvement defined as decrease in NAFLD Activity Score (NAS) of ≥2 points with no worsening in fibrosis

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**FLINT Trial Design**

N=283 Patients w/ Histological Evidence of NASH*

- **OCA 25 mg QD**
  - Follow-up
- **Placebo QD**
  - Follow-up

Screening (Biopsy) → 72-week treatment period → 24 week off treatment

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*Entry was based upon histologic diagnosis of nonalcoholic steatohepatitis (NASH) based on local CRN site pathologist’s read (end-of-study blinded central read of baseline biopsies revealed 80% of patients enrolled had definite NASH); interim analysis was conducted when ≥50% of patients completed treatment and had repeat liver biopsy; NAFLD: nonalcoholic fatty liver disease; Neuschwander-Tetri B, et al. *Lancet*. 2014:S0140-6736(14)61933-4; Neuschwander-Tetri B, et al. Presented at EASL, 50th annual meeting; 2015; Vienna, Austria (Poster LB18).
FLINT Study: Improved Liver Histology After 72 Weeks of Treatment

**Endpiont** | OCA 25 mg | Placebo | P-value
---|---|---|---
Fibrosis Improvement (%) | 35% | 19% | 0.01
Hepatocellular Ballooning (%) | 46% | 31% | 0.03
Steatosis (%) | 61% | 38% | 0.001
Lobular Inflammation (%) | 53% | 35% | 0.007
NASH Resolution (%) | 22% | 13% | 0.08

**Lipid Parameters Measured** (*p<0.05, all p-values compared to placebo)

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OCA</td>
<td>Placebo</td>
<td>OCA</td>
<td>Placebo</td>
</tr>
<tr>
<td>Baseline</td>
<td>190</td>
<td>197</td>
<td>112</td>
<td>111</td>
</tr>
<tr>
<td>Δ Base-72 wks (n=240)</td>
<td>+6*</td>
<td>-7*</td>
<td>+9*</td>
<td>-8*</td>
</tr>
<tr>
<td>Δ Base-96 wks (n=240)</td>
<td>-12</td>
<td>-8</td>
<td>-12</td>
<td>-12</td>
</tr>
</tbody>
</table>

Adverse Events

- 6 severe adverse events in obeticholic acid group
  - 4 severe pruritus (1 stopped treatment)
  - 1 hypoglycemia
  - 1 possible cerebral ischemia (dysarthria and dizziness)
- Moderate or severe pruritus
  - 23% in obeticholic acid
  - 6% in placebo

\[ P < 0.0001 \]

Summary - NAFLD and NASH

- NAFLD is a complex disease tied closely to obesity and diabetes
- NASH patients with fibrosis most likely to progress
  - NAFLD/NASH in the setting of DM/MS has adverse outcomes
- Personalized targeted treatment best to treat NASH
- Some considerations for current patients with NASH
  - Life style modifications for all
  - Vitamin E for non-DM NASH
  - Pioglitazone for DM with NASH but be aware of safety concerns
  - Clinical trials (OCA and others)
  - Consider bariatric surgery for morbidly obese+/-DM with NASH
- Multiple clinical trials underway in the US to treat NASH