Nonalcoholic fatty liver disease (NAFLD)

- Dawn McDowell Torres, MD
- Chief, Gastroenterology
- Walter Reed National Military Medical Center
Disclosure of Financial Relationships

Dawn M. Torres, MD

Has disclosed relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

Research Grants/Contracts

Abbvie, Galectin, Gilead, Intercept, Immuron

Speaker’s Bureau

None
Objectives

- Describe the primary etiologies of chronic hepatitis today and predictions for the future face of liver disease
- Understand the criteria required for the diagnosis of NAFLD and NASH
- Outline the current available treatments for NAFLD and NASH
QUESTION

What is the most common chronic liver disease in the US?

A) Chronic hepatitis C
B) Autoimmune hepatitis
C) Chronic hepatitis B
D) Non-alcoholic fatty liver disease
E) Drug induced liver disease
D) Non-alcoholic fatty liver disease

Most common cause of liver disease globally. In U.S. prevalence is estimated at 30-40%
Case #1: 55 year old Hispanic female

- **ROS:** N/V/F/C. Occasional vague RUQ pain not assoc w/meals, BMs. No diarrhea, constipation, blood in stool.

- **ROS:** 20 lbs wt gain over 5 years

- **PMH:** DM Type 2, HTN, HLD, OSA, GERD

- **PSH:** Lap chole 2010 & TAH Hysterectomy 2005

- **Soc:** 1-2 drinks per week, no tobacco

- **Family History:** Grandmother with cirrhosis

- **Meds:** Metformin, Lisinopril/HCTZ, Atorvastatin, Aspirin, Prilosec
Case #1: 55 year old Hispanic female with asymptomatic elevation of her liver enzymes

- **Physical exam:** HR 86, BP 137/80, RR 12, SPO2=98%
  RA, T 98.4, BMI 32.5
- Gen: Obese Hispanic female in NAD, A/Ox3, conversant & cooperative
- Lungs: CTA
- Cardio: RRR
- Abd: obese with well healed surgical scars. Liver palpable 3 cm below costal margin, spleen nonpalpable, nontender
- Extremities: no stigmata of liver disease, no pedal edema, no rashes
Case #1: 55 year old Hispanic female with asymptomatic elevation of her liver enzymes

- Basic labs:
  - CBC: WBC 7, HCT 39, platelets 170
  - INR 1.0
  - Alk phos 80  AST  52  ALT  74  T bili 0.4
  - TP 7.8, Albumin 3.9
Case #1: 55 year old Hispanic female

- What additional information would be helpful?
Case #1: 55 year old Hispanic female

- **Helpful additional information:**
  - Duration of liver enzyme elevation
  - Supplements or herbals
  - Risk factors for viral hepatitis – tattoos, IVDU or intra-nasal cocaine, high risk sexual behavior (anal intercourse, multiple partners), blood transfusion 1990s or earlier
  - Etiology of cirrhosis of grandmother
  - Health care maintenance: colonoscopy, pap/mammogram
Case #1: 55 year old Hispanic female with asymptomatic elevation of her liver enzymes

- What is your differential diagnosis?
- What labs and imaging studies should be ordered?
- Is a liver biopsy indicated?
Differential diagnosis: asymptomatic mild-moderate hepatocellular liver enzyme elevation

- NAFLD
- Alcohol related liver disease
- Viral Hepatitis (B, C)
- Autoimmune hepatitis
- Drug induced liver injury
- Hemochromatosis
- Alpha-one anti-trypsin deficiency
- Thyroid dysfunction, Celiac
Case 1: Additional information

- Hgb A1c 7.5
- Hep C Antibody negative
- Hep B core Ab neg, surface Ag neg, surface antibody positive
- ANA neg, IgG normal
- TTG negative, total IgA normal
- TSH normal
- Ferritin & iron panel normal
- RUQ US with hepatic steatosis
Non-alcoholic fatty liver disease: Basic definitions

All pts with fatty liver

Liver biopsy

Isolated fatty liver

Non-alcoholic steatohepatitis (NASH): fat + inflammation +/- fibrosis

Increased risk: Cirrhosis & Liver cancer

**Alcoholic steatohepatitis (ASH) cannot be differentiated from NASH on biopsy, history is critical
NAFLD Clinical Associations

- Cardiovascular disease
- OSA
- Pancreatic steatosis
- Vitamin D deficiency
- Hypothyroidism
- Diabetes
- Elevated ferritin
- PCOS
- Adenomatous polyps
- Hyperuricemia

Natural History of NAFLD

NAFLD

*~80%

Isolated fatty liver

1. None to very minimal progression to cirrhosis
2. No increased risk of death compared with the general population

NASH

~11% over 15 years, but significant variability

HCC

~7% over 6.5 years

NASH Cirrhosis

~31% over 8 years

Decompensation

1. Increased risk of death compared with general population. Causes of death, in order:
   a. Cardiovascular
   b. Malignancy
   c. Liver-related
2. NASH with fibrosis portends worse prognosis
   a. Fibrosis progression associated with DM, severe IR, BMI, weight gain >5kg, rising ALT, AST, cigarette smoking

Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory 2014
NAFLD Prevalence


<table>
<thead>
<tr>
<th>Category</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD overall</td>
<td>46%</td>
</tr>
<tr>
<td>NAFLD Hispanic</td>
<td>30%</td>
</tr>
<tr>
<td>NAFLD Caucasian</td>
<td>45%</td>
</tr>
<tr>
<td>NAFLD African American</td>
<td>44.4%</td>
</tr>
<tr>
<td>NAFLD African American</td>
<td>33%</td>
</tr>
<tr>
<td>NASH overall</td>
<td>35.1%</td>
</tr>
<tr>
<td>NASH overall diagnosed NAFLD</td>
<td>24%</td>
</tr>
<tr>
<td>NASH among diagnosed NAFLD</td>
<td>12.2%</td>
</tr>
<tr>
<td>NASH overall</td>
<td>29.9%</td>
</tr>
</tbody>
</table>
High risk patients

- Diabetic
- Hispanic
- BMI > 28
- AST/ALT ratio ≥ 0.8
- Co-existing liver disease
  - Alcohol use
  - Hepatitis C
Who to biopsy?

- Diagnostic dilemma
- High risk
  - Non-invasive risk stratification
    - NAFLD fibrosis score, BARD score, etc
    - Fibroscan, MR Elastography, etc
- Failed lifestyle modification
Case 1: Additional information

- **NAFLD fibrosis score:** 2.00
  - <-1.455 predicts F0-1 fibrosis
  - <-1.455 to <0.675 indeterminate
  - >0.675 predicts significant fibrosis

- **Fibroscan:** 9 kPascals
Liver biopsy: Stage 3 NASH
Case 1: Stage 3 NASH...Now what?

- What is the optimal treatment for NAFLD patients?
  - **Diet/exercise**
    - Surgical
    - Pharmacotherapy
Pathogenesis of NASH with Potential Sites for Therapy

NAFLD: Dietary Characteristics

- ↑ saturated fat/cholesterol and ↓ polyunsaturated fat, fiber and antioxidant vitamins C and E\(^1\)
- ↑ intake of soft drinks and meat, but ↓ omega-3 fatty acids \(^2\)
- ↑ Overall energy intake\(^3\)
- High fructose diets may also contribute to NAFLD\(^4\)

2. Zelber-Sagi S, J Hepatol 2007
Weight Loss

- **Effective**
  - 9-10% body weight loss
  - improved insulin sensitivity, liver enzymes, hepatic steatosis, ballooning degeneration, & lobular inflammation

- **Sustainability??**
  - 1310 patients lost 10% weight 1999-2002 NHANES study
  - 66.5% maintained or reduced weight
  - Sedentary lifestyle $\rightarrow$ inability to maintain weight loss

Exercise

- Moderate exercise, expending 400-kcal/session, 3 times/week $\rightarrow$ ↑insulin sensitivity
- Overall energy expenditure achieved per work-out more important than intensity
- Aerobic or resistance training both of benefit
Bariatric Surgery

- Duodenal switch procedure
- Adjustable gastric banding
- Roux-en-Y gastric bypass
- Gastric sleeve
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Surgery</th>
<th>Mean WT Δ</th>
<th>Steatosis Improvement</th>
<th>Pericellular Fibrosis Change</th>
<th>Hepatocellular Injury</th>
<th>NASH Resolved</th>
<th>Histopathologic Worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon et al 68</td>
<td>LAGB</td>
<td>34 kg</td>
<td>Significant (p&lt;0.001)</td>
<td>91% improvement; 70% resolution</td>
<td>100%</td>
<td>82%</td>
<td>None</td>
</tr>
<tr>
<td>de Almeida et al 73</td>
<td>RYGBP</td>
<td>22.3 kg</td>
<td>75% resolution</td>
<td>50% improvement</td>
<td>69% resolution</td>
<td>94%</td>
<td>None</td>
</tr>
<tr>
<td>Barker et al 72</td>
<td>RYGBP</td>
<td>18 kg</td>
<td>100%</td>
<td>47% improvement</td>
<td>Improvement</td>
<td>89%</td>
<td>10.5% mild fibrosis increase</td>
</tr>
<tr>
<td>Mattar et al 71</td>
<td>RYGBP (41) LSG (23)</td>
<td>46.8 kg</td>
<td>37% complete resolution</td>
<td>20% complete fibrosis resolution</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Mathurin et al 69</td>
<td>BIB, LAGB</td>
<td>27 kg</td>
<td>Significant p&lt;0.001</td>
<td>0.14 to 0.38 (p=0.0001)</td>
<td>NA</td>
<td>75%</td>
<td>Mild fibrosis ↑ 1 year</td>
</tr>
<tr>
<td>Mottin et al 75</td>
<td>RYGBP (Majority)</td>
<td>NA</td>
<td>82.2% (54% resolution)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>et al 74</td>
<td>RYGBP</td>
<td>53.7 kg</td>
<td>81% resolution</td>
<td>43%</td>
<td>86%</td>
<td>81%</td>
<td>None</td>
</tr>
<tr>
<td>Furuya et al 70</td>
<td>RYGBP</td>
<td>19.3 kg</td>
<td>84% resolution</td>
<td>75% resolved fibrosis</td>
<td>50%</td>
<td>No pts NAS of &gt;4</td>
<td>None</td>
</tr>
<tr>
<td>Liu X et al 76</td>
<td>RYGBP</td>
<td>50.2 kg</td>
<td>97% resolved macrosteatosis</td>
<td>Fibrosis ↓: 50% → 25%</td>
<td>100%</td>
<td>100%</td>
<td>2.5% mild fibrosis</td>
</tr>
<tr>
<td>Kral et al 67</td>
<td>BPD</td>
<td>38 kg</td>
<td>↓ grade 1.57 to 0.52 (p&lt;0.0001)</td>
<td>Severe 27%; mild 40%</td>
<td>NA</td>
<td>NA</td>
<td>Mild fibrosis ↑ over &gt; 3 years</td>
</tr>
<tr>
<td>Csendes et al 77</td>
<td>RYGBP</td>
<td>15.7 kg</td>
<td>93%</td>
<td>4/5 (80%)</td>
<td>5/5 (100%)</td>
<td>100%</td>
<td>6.7% (mild)</td>
</tr>
</tbody>
</table>

Bariatric Surgery

- Newer procedures improve NASH histology
- Consider if comorbid conditions that would warrant morbidity/mortality of surgery
Pharmacotherapy

- Weight loss medications
- Insulin sensitizers/diabetic medications
- Anti-oxidants
- Anti-fibrotic agents
Orlistat

- Reversible inhibitor of gastric & pancreatic lipase
- Blocks 30% of fat absorption
- 5-10% ↓ body weight w/6-12 months tx
- Zelber-Sagi \(^1\)
  - 44 pts randomized, double-blind: 6 months of orlistat or placebo
  - Serum ALT 48% versus 26.4% improvement
  - No histology
- Hussein\(^2\)
  - 14 NASH pts tx 6 months
  - 10 pts ↓ steatosis (70%, p<0.01)
  - Necroinflammation
    - 28% 2 grade improvement
    - 50% 1 grade improvement
    - 22% no change
Incretin mimetics and enhancers

- Intestinal glucose load $\rightarrow$ activation of GIP and glucagon-like peptide (GLP-1) $\rightarrow$ insulin secretion
  - Pathway deficient in type 2 diabetes

- 2 types:
  - Direct GLP-1 mimetic
    - Exenatide
  - DPP-4 inhibitors
    - Sitagliptin
    - Vildagliptin

Byetta

- Pilot trial (n=9) for 6 months
  - modest weight loss
  - improvement in hepatic steatosis
- Side effect nausea
- Larger RCTs in progress with weekly extended release formulation (bydureon) in progress

DPP-4 inhibitors

- Improves fasting glucose & insulin in diabetic pts
- Neutral effect on weight loss
  - 1 study with modest wt gain
- Not studied in NAFLD
- Sitagliptin
- Vildagliptin
- Linagliptin
- Alogliptin
Diabetic medications

- Thiazolinediones (TZDs)
  - Avandia
  - Actos
- Metformin
Pioglitazone

- Thiazolidinedione (TZD) = selective peroxisome proliferator-activated receptor-gamma agonist
- $\uparrow$ insulin sensitivity
  - adipose tissue, muscle, liver
- Approved for diabetes treatment
- Well studied in NASH
## Major studies with histologic endpoints

<table>
<thead>
<tr>
<th>Author, Year, Name</th>
<th>Length</th>
<th>Dosing</th>
<th>N (Tx + Placebo)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belfort 2006</td>
<td>6 months</td>
<td>Pioglitazone 45 mg/d</td>
<td>26+21</td>
<td>Pioglitazone ↓ fibrosis &amp; inflammation not placebo</td>
</tr>
<tr>
<td>Ratziu 2008 (FLIRT)</td>
<td>12 months</td>
<td>Rosiglitazone 4mg/d → 8 mg/d</td>
<td>32+31</td>
<td>Rosiglitazone ↓ steatosis but not fibrosis, ballooning, inflammation</td>
</tr>
<tr>
<td>Aithal 2008</td>
<td>12 months</td>
<td>Pioglitazone 30 mg/d</td>
<td>37+37</td>
<td>Pioglitazone ↓ fibrosis, injury more than placebo but not steatosis, inflammation</td>
</tr>
<tr>
<td>Sanyal 2010 (PIVENS)</td>
<td>96 weeks</td>
<td>Pioglitazone 30 mg/d</td>
<td>80+83</td>
<td>Pioglitazone no better than placebo for fibrosis, NAS but did resolve NASH&gt;placebo (or Vit E)</td>
</tr>
</tbody>
</table>

Modified from: Singh S et al.. Hepatology 2015.
Pioglitazone

- The pro’s
  - ↓ insulin resistance
  - Improves hepatic histology albeit modest fibrosis benefit
  - Previous concerns of bladder cancer likely unwarranted\(^1\)

- The con’s
  - Weight gain (5-10 pounds)
  - Bone fractures in diabetics\(^2\)
  - CHF Black box warning (rare)
  - Benefits short-lived after discontinuation of therapy

---

Pioglitazone

- Tri-society guidelines (AASLD, ACG, AGA):
  - Pioglitazone can be used to treat steatohepatitis in biopsy proven NASH patients. However it should be noted that the majority of the patients used in clinical trials were non-diabetic and long term safety/efficacy is not established for NASH.¹
  - Consider in diabetic NASH patients without heart failure who can tolerate modest weight gain

Metformin

- Biguanide improves insulin sensitivity
  - Decreases hepatic gluconeogenesis
  - Limits triacylglycerol production
- Promising studies in animals
- Mixed results in adult NAFLD
  - Improves hepatic steatosis
  - No significant improvement in fibrosis & necroinflammation
Vitamin E

- Free radical scavenger & antioxidant
- Multiple RCTs with variable endpoints
- Liver associated enzymes improve
  - Meta-analysis 4 NAFLD studies¹
    - AST ↓ 19.43 U/L and ALT ↓ 28.91 U/L

¹Sato K et al. Nutrition 2015;31:923-930
## Major studies with histologic endpoints

<table>
<thead>
<tr>
<th>Author, Year, Name</th>
<th>Length</th>
<th>Dosing</th>
<th>N (Tx + Placebo)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison 2003</td>
<td>6 months</td>
<td>Vit E 1000 IU/d &amp; Vit C 1000 mg/d</td>
<td>25+24</td>
<td>Vit E/C superior to placebo for fibrosis score but NOT inflammation/necrosis</td>
</tr>
<tr>
<td>Sanyal 2010 (PIVENS)</td>
<td>96 weeks</td>
<td>Vit E 800 IU/d</td>
<td>84+83</td>
<td>Vit E improved ballooning, NAS, no Δ fibrosis</td>
</tr>
<tr>
<td>Lavine 2011 (TONIC)</td>
<td>96 weeks</td>
<td>Vit E 800 IU/d</td>
<td>58+58</td>
<td>Vit E improved NAS, induced resolution of NASH (58% v 28%)</td>
</tr>
</tbody>
</table>

Meta-analysis Vitamin E versus placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>0.93 (0.79, 1.09)</td>
</tr>
<tr>
<td>Ballooning degeneration</td>
<td>0.73 (0.61, 0.81)</td>
</tr>
<tr>
<td>Steatosis</td>
<td>0.73 (0.59, 0.89)</td>
</tr>
<tr>
<td>Lobular Inflammation</td>
<td>0.82 (0.62, 1.09)</td>
</tr>
</tbody>
</table>

Vitamin E Potential Risks

- ↑ all-cause mortality with high dose Vit E $^{1,2}$
- 400 IU/day ↑ risk prostate cancer $^3$
  - Absolute increase 1.6 per 1000 person yr of Vit E use

$^3$Klein EA et al. JAMA 2011;306,1549-56.
Vitamin E

- Tri-society guidelines (AASLD, ACG, AGA) recommend Vit E for non-diabetic NASH patients\(^1\)
- Reasonable to consider Vit E 400-800 IU once daily for non-diabetic NASH patients

\(^1\)Chalasani N et al. Gastroenterology 2012;142:1592-1609.
Pentoxyfylline

- Nonspecific phosphodiesterase inhibitor shown to ↓ TNF-α
- Used to treat claudication
- Has been studied in NASH\(^1\)

\(^{1}\)Li W et al. Lipids Health Dis 2011;10:49.
## Pentoxyfylline (PTX)

<table>
<thead>
<tr>
<th>Author, Year, Name</th>
<th>Length</th>
<th>Dosing</th>
<th>N (Tx + Placebo)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Wagner 2011</td>
<td>12 months</td>
<td>PTX 400 TID</td>
<td>21+9</td>
<td>PTX improved NAS but not superior to placebo in resolving NASH (44% v 28%)</td>
</tr>
<tr>
<td>Zein 2011</td>
<td>12 months</td>
<td>PTX 400 TID</td>
<td>26+29</td>
<td>PTX improved NAS by 2 pts (38.5% v 13.8%) and resolved NASH &gt; placebo (25% v 3.9%)</td>
</tr>
</tbody>
</table>

Pentoxifylline

- Moderate quality evidence to support ↓ steatosis, fibrosis, lobular inflammation
- Not mentioned in tri-society practice guidelines
- Safe medication
- GI side effects: nausea and/or vomiting
- Consider in patients not eligible for Vit E or Pioglitazone
Statins

- NASH pts often have ↑ lipids
- Statins=3-hydroxy-3-methyl-glutaryl coenzyme-A reductase (HMGCR inhibitors) → prevention of CV events & ↓ lipids
- ? Statin efficacy for treatment of NASH

1 Van Rooyen DM et al. Gastroenterology 2011;141:1393-1403.
Statins

- Many NAFLD patients meet tx guidelines for statin therapy for CV benefit:
  - NAFLD pts also have ↑ LAEs, statins may further ↑ LAEs but RARELY cause serious liver disease

- STATINS ARE SAFE TO USE IN NAFLD/NASH

Statins

- Although safe, data on efficacy for NASH is limited, non-prospective, & usually without hepatic histology
Statins

- Tri-society guidelines recommend statins for dyslipidemia in NASH patients but not specifically to treat NASH
- Use for hyperlipidemia in NASH, with some possible benefit for NASH although not confirmed
Caffeinated Coffee & NAFLD

Investigational therapies

- **Anti-fibrotic**
  - Simtuzumab → Study terminated for lack of efficacy

- **Anti-inflammatory**
  - Elafibranor
  - Cenicriviroc
  - Galectin-3 antagonists
  - NOX-1 and NOX-4 inhibitors

- **Hepato-protective**
  - Farnesoid X nuclear receptor ligand
  - PPAR-α/δ agonist
  - Pan-caspase protease inhibitor

Noureddin M et al. AP&T. June 2016
Obeticholic acid (OCA)
(Farnesoid X nuclear receptor ligand)

- FLINT trial
- OCA improved NAS, ballooning, steatosis, lobular inflammation more than placebo
- Pruritus (33% versus 9% any itching)
- Lipid effects (↑ LDL)

Adult NAFLD algorithm

- Fatty liver imaging or Elevated LFTS
  - Concern for NASH: risk factors additive
    - Age>50
    - Obesity
    - AST:ALT ratio>0.8
    - Non-African American
    - Low platelets count
  - Rule out other causes liver disease
    - No obvious causes of secondary steatosis (i.e. alcohol, meds)
    - Presence of insulin resistance or DM
  - +/− trial of diet, exercise, vitamin E 400 IU Q24

Liver biopsy

Isolated fatty liver (IFL)
- ↓ daily caloric intake 500 kCal
- Diets ↑ MUFA, PUFA & ↓ in processed carbohydrates & SFA
- Exercise 4x per week: Burn 400 kCal each time

NASH
- Lifestyle changes (same as IFL)
- Consider:
  - Clinical treatment trials (clinicaltrials.gov)
    - Pentoxifylline
    - Vitamin E (nondiabetic)
    - Incretin mimetics (byetta)
    - Thiazolidinediones (TZDs) in diabetic patients
    - Bariatric surgery: roux-en-Y gastric bypass or lap band (with comorbid conditions)

MUFA=mono-unsaturated fatty acid, PUFA=poly-unsaturated fatty acid, SFA=saturated fatty acid

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect</th>
<th>Side Effects/Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E 800–1000 IU daily</td>
<td>Improves NASH when used for 2 years. No fibrosis benefit.</td>
<td>Validation studies in diabetics and various ethnic groups needed to confirm benefit. May increase risk of prostate cancer.</td>
</tr>
<tr>
<td>Pioglitazone 30–45 mg daily</td>
<td>Improves NASH when used for 6 months to 2 years. May have a fibrosis benefit based on recent meta-analysis.</td>
<td>Expect a 4kg weight gain, possible increased risk for CHF and osteoporosis. Not FDA approved for NASH treatment. Limit use to those with stage 2 fibrosis or greater who failed an adequate challenge with diet and exercise.</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>Improves NASH and fibrosis.</td>
<td>Small pilot trial data. Need confirmation in large, multi-centered trial.</td>
</tr>
<tr>
<td>Statins</td>
<td>Limited data on histopathology</td>
<td>Safe in NAFLD patients. Reduces risk of cardiovascular disease</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RYGB, LAGB, sleeve gastrectomy</td>
<td>Improves or resolves NASH in 60–80% of cases. Likely fibrosis benefit as well</td>
<td>Lack of randomized, controlled trials. Caution in cirrhotic patients. Lifestyle modification attempted first.</td>
</tr>
</tbody>
</table>
Case 1: Summary

- NAFLD most common cause of chronic liver disease
- NASH patients at risk of developing cirrhosis and have higher all cause mortality
- No FDA approved medications for NAFLD
  - Vitamin E 400 IU once daily
  - Actos 15-45 mg once daily for advanced disease
- Bariatric surgery can be effective
- **Lifestyle modification remains cornerstone of therapy**
Case 2: 64 yo Caucasian male with new onset abdominal swelling

- ~1 month of progressive abdominal swelling and mild LE edema
- +Mild early satiety as he feels fuller with small meals coincident with the abdominal distention
- 7 pound weight gain in the last 2 weeks
- Negative:
  - SOB, chest pain, GIB, change in bowel habits, N/V/F/C
Case 2: 64 yo Caucasian male with new onset abdominal swelling

- **PMH**: Type 2 Diabetes, HTN, HLD, ASCAD, GERD
- **PSH**: 3V CABG 2013, Lap chole
- **SOC**: no EtOH or tobacco
- **HCM**: EGD for GERD 2011 – normal except for 2 cm hiatal hernia, Colo x 2 – no polyps (most recent 2011), TTE 2016 – normal overall, EF 65% (hyperdynamic)
- **Family history**: no liver disease or colon cancer
- **MEDS**: metformin, lantus insulin, aspirin 81, lisinopril/HCTZ, prilosec
Case 2: 64 yo Caucasian male with new onset abdominal swelling

- **PE:** BP 104/64 HR 82 T 98.4 RR 12 SPO2=97% on RA, BMI 38
- **Gen:** pleasant male in NAD, conversant, articulate & cooperative
- **Lungs:** CTA
- **Cardio:** RRR with no M/G/R. 1+ LE edema bilaterally to mid-shin
- **Abd:** obese & protuberant with +fluid wave, easily reducible 2x3 cm umbilical hernia, normal bowel sounds, non-tense
- **Extremities:** no rashes, no asterixis
Case 2: 64 yo Caucasian male with new onset abdominal swelling

**Labs:**
- WBC 4  HCT 37  platelets 54
- Normal BMP (Bun 12/creat 0.7)
- Alk 67  AST 40  ALT 38
- TP 7, Alb 3.3
- INR 1.1
Case 2: 64 yo Caucasian male with new onset abdominal swelling

- What additional testing if any should be done?
- Is a liver biopsy indicated?
New onset ascites

- Abdominal imaging
- Diagnostic Paracentesis
- Complete serologic work-up for liver disease (see first case)
Liver Cancer Screening

- US or 3-phase contrast cross sectional imaging (CT or MRI)
- Serum AFP removed from guidelines
Surveillance for HCC: AASLD Recommendations

- Population in which surveillance should be done
  - Hepatitis B
    - Asian males > 40
    - Asian females > 50
  - Family hx of HCC
  - African/North American Blacks > 20
  - Cirrhotics
  - Hepatitis C cirrhosis
  - PBC, stage 4
  - Hereditary Hemochromatosis, stage 4
  - Alpha 1-antitrypsin Deficiency, stage 4
  - Other cirrhosis

Unsure:
- HBV younger than 40 for men and 50 for women
- HCV, stage 3
- Non-cirrhotic NAFLD

Bruix and Sherman. Hepatology 2010
Summary  Case #2

- NAFLD most common cause of chronic liver disease & growing cause of cirrhosis
- NASH cirrhosis set to become #1 indication for liver transplant in next 20 years
- New onset ascites requires paracentesis
- NASH cirrhotics should be treated similar to cirrhosis from other etiologies