Non-Alcoholic SteatoHepatitis (NASH): Identification & Evolving Treatment Strategies

Faculty

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Disclosures

- Kalyan R. Bhamidimarri, MD, MPH has no relevant relationships to disclose.
Learning Objectives

After participating in the proposed educational activities, clinicians should be better able to:

1. Identify patients at high risk for nonalcoholic fatty liver disease (NAFLD)
2. Distinguish non-alcoholic fatty liver (NAFL) from nonalcoholic steatohepatitis (NASH) and understand how to stage the disease
3. Implement ongoing evidence based general management of patients with NASH
4. Describe the available and emerging treatment options for patients with NASH

PRE-TEST QUESTIONS

Pre-test ARS Question 1

On a scale of 1 to 5, please rate how confident you would be treating a patient with non-alcoholic steatohepatitis:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-test ARS Question 2
Which of the following patients are not at high risk for the development of NAFLD:

1. Patient with Rheumatoid arthritis taking methotrexate for > 10 years
2. Obese woman who lost 100lbs after jejuno-ileal bypass (bariatric surgery)
3. Man with BMI 35 who has DM2 and OSA
4. Young boy with Crohn's s/p multiple intestinal resections on TPN
5. Middle aged woman with colon cancer in cecum s/p hemicolectomy

Pre-test ARS Question 3
CASE
62 year old Caucasian man with Obesity (BMI 45), DM2, Hypertension, Hyperlipidemia, Obstructive Sleep Apnea, and Osteoarthritis of the knees has mildly elevated LFT’s in the past which were attributed to him being on statins. Despite all efforts to lose weight, the patient was able to lose only 2% of his weight due to his limited exercise capacity. Ultrasound demonstrates increased echogenicity of the liver suggestive of fatty liver.

Pre-test ARS Question 3
What is the current gold standard to distinguish NAFLD from NASH:

1. Liver biopsy
2. LFT's
3. Ultrasound
4. MR Spectroscopy
Pre-test ARS Question 4

CASE

68 year old Hispanic woman with Metabolic syndrome has new onset ascites and was hospitalized recently for fluid overload. Blood tests show serum albumin of 2.4, platelets of 98k and upper endoscopy which showed grade 2 varices. She underwent a transjugular liver biopsy which shows stage 4 fibrosis.

Pre-test ARS Question 4

CASE

Given the clinical picture which is consistent with decompensated cirrhosis, how would you screen the patient for hepatocellular carcinoma?

1. MRI abdomen every 2 years
2. CT scan abdomen & pelvis every 2 years
3. Ultrasound abdomen every 6 months
4. Fibroscan every year
5. All the above

Pre-test ARS Question 5

CASE

55 year old non-diabetic woman is recently diagnosed with NASH and advanced fibrosis (stage 3) on liver biopsy. You recommend aggressive life-style modifications but the patient was unable to lose > 1% of her body weight over a period of 1 year.
Pre-test ARS Question 5

Given the presence of advanced fibrosis in the setting of NASH, which of the following additionally would you recommend in her management that would improve her liver histology?

1. Metformin
2. Orlistat
3. Cholecystectomy
4. Vitamin E
5. Ursodiol

Edward, a 55-year-old obese male BMI 35 kg/m² with borderline diabetes went to his PMD. Upon his suggestion, he started a crash diet and “ORANGE CRUSH” exercise program. He lost 60 lbs in 6 months. Denies drinking. His mother died of end-stage liver disease of uncertain etiology.

His laboratory tests revealed the following: AST 106, ALT 118, with normal bilirubin, alkaline phosphatase and prothrombin time.

A liver ultrasound showed diffusely echogenic liver.

What do you suspect?

1. Surreptitious drinking
2. NAFLD
3. DILI
4. Viral Hepatitis
NAFLD: Etiology Spectrum

- Metabolic Syndrome
- Starvation/PEM
- TPN
- Drugs: Amiodarone, Diltiazem, Chemorx, Methotrexate, HIV - PI
- Lipodystrophy: Congenital or Acquired
- Celiac disease
- Short Bowel Syndrome: Jejun-ileal bypass
- Genetic disorders: Atp7a, Ldlr, Atp5a1
- Weber-Christian Syndrome
- Chronic Inflammation: RA, GLS

NAFLD Phenotype Spectrum

NAFLD Host Spectrum
NAFLD Pathologic Spectrum

- NAFL (nonalcoholic fatty liver)
  - Excess fat accumulation (steatosis)
- NASH (nonalcoholic steatohepatitis)
  - Defines a subgroup within NAFL
  - Steatosis co-exists with liver cell injury and inflammation
- Cirrhosis/ESLD
  - Liver decompensation
  - Portal HTN

NASH: Histologic Spectrum

- Microvesicular
- Macrovesicular
- Mixed Steatosis

ARS Question

Do you think obesity/NAFLD is:
1. Endemic
2. Epidemic
3. Pandemic
4. Hereditary
True Incidence & Prevalence of NAFLD: Unknown

- Heterogeneous data: population, race, alcohol inclusion
- Inconsistent
  - Clinical definitions
  - Competing etiologies
  - Diagnostic techniques
  - Histologic parameters
- Under-diagnosis
- Under-appreciation
- Unawareness

NAFLD Prevalence

NASH Prevalence: Ethnicity
NAFLD Risk Factors for Progression

Risk Factors for NAFLD

Non-Modifiable
- Age: Older
- Gender: Men, Postmenopausal women (esp. Caucasian)
- Race: Higher in Hispanics/Native Indian
- Genetic: PNPLA3 mutation
- Baseline Histology

Modifiable
- Obesity
- Insulin Resistance
- DM2
- Dyslipidemia
- Lifestyle: Diet, Sedentary, Alcohol, Smoking

Metabolic Syndrome: NAFLD/NASH is the hepatic manifestation
Obesity Prevalence: US Adults

Diabetes not only increases risk of NASH but also of HCC

Diabetes N=173,543
No Diabetes N=650,620

NASH: Genetics

- 2 Candidate genes identified by Genome Wide Association Studies (GWAS)
  - TM6SF2: lipid transporter gene
  - PNPLA3: Stronger genetic determinant (p < 10^-9)

- Patients with PNPLA3 mutation (SNP): High rates of
  - Steatosis
  - Inflammation
  - Fibrosis

PNPLA3: Patatin like phospholipase
SNP: Single nucleotide polymorphism
NAFLD: Prognosis

NAFLD → NASH → Cirrhosis → Decompensated cirrhosis → HCC

NAFLD: Clinical Presentation

Asymptomatic
- Abnormal LFT's
- Fatty liver on imaging

Symptomatic
- Non-Specific Symptoms: Fatigue, Hepatomegaly, Pruritis
- Liver Related: Decompensated cirrhosis, Hepatocellular carcinoma
- Extrahepatic: CVS risks, Malignancy (GI, Renal, Breast), Chronic Kidney Disease, Diabetes

ARS Question

Are there any blood tests to assess NAFLD/ NASH?

1. Yes
2. No
3. Don't Know
Non-Invasive Tests

- Non-Invasive Tests
  - Fibrosis
    - Fibrometer
    - NAFLD fibrosis score
    - Fib-4
    - APRI
    - BARD
    - AST/ALT ratio
    - Fibrotest
    - ELF (European liver fibrosis
      Markers of extracellular matrix)
    - Fibroscan
    - ARFI (acoustic radiation force
      impulse): US based technique
    - MR Elastography
  - Steatosis/Steatohepatitis
    - Caspase cleaved CK-18
    - Soluble Fas
    - M65 (Caspase cleaved and uncleaved proteins)
    - ALT
    - HOMA score

Steatosis: Ultrasound

- Normal Liver: Echogenecity similar to R-Kidney cortex
- Fatty Liver: Liver more echogenic than R-Kidney cortex
  - Less of portal vessel outlines

Steatosis: CT Scan

- Normal Liver: Non-contrast: hyperdense > vessels
  - C +/-: Liver hyperdense > Spleen
- NAFLD/ NASH: Liver density < Spleen/ Vessels
Inflammation will avoid need for liver populations (morbidly obese patients) and have not been HAIR (hypertension, increased ALT, and IR), NashTest was 0.84.

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Specifcity.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; AST/ALT ratio, aspartate transaminase/alanine transaminase ratio; BMI, body mass index; CK-18, keratin 18; C21, C20/C0, C2, CK-18, keratin 18; CT, computed tomography; DFS, disease-free survival; FIB-4, fibrosis-4; FibroTest, a proprietary test; GGT, gamma-glutamyl transpeptidase; IFG, impaired fasting glucose; LS, liver stiffness; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; P, p-value; P3, alogarithmic coefficient; ROC, receiver operating characteristic; Se, sensitivity; Sp, specificity; TIMP-1, tissue inhibitor of metalloproteinase-1; V, variance; W, weight; x, x-intercept; y, y-intercept; X, x-value; Y, y-value; Z, z-value.

Serum markers of NASH

- NASH \( \Rightarrow \) Inflammation \( \Rightarrow \) Apoptosis
- Apoptosis markers: correlate inflammation
- Apoptosis mediated by caspase-3 cleaves CK 18
- CK-18 abundant in hepatocytes
- Others: M30, M65, M65ED

Non invasive markers of NASH: inflammation will avoid need for liver biopsies: Extensive Research ongoing.

Fibrosis: Serum Tests

<table>
<thead>
<tr>
<th>Prediction score</th>
<th>Patients (n)</th>
<th>Variables/formula</th>
<th>Cutoff</th>
<th>Se (%)</th>
<th>Sp (%)</th>
<th>AUC</th>
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<td>HCC</td>
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<td>97</td>
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<td>( y = 0.88 0.0102 x + 0.037 )</td>
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<td>82</td>
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<tr>
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<td>90</td>
<td>97</td>
<td>0.93</td>
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<tr>
<td>270</td>
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<td>0.93</td>
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<td>250</td>
<td>192</td>
<td>( y = 0.88 (ln(HA) + 0.0459 x + 0.037 )</td>
<td>0.037</td>
<td>90</td>
<td>97</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Limitations:
- Small 2d Voxel
- Need number of corrections
- Not widely available
- Expensive
Fibrosis: Serum Tests

- Well studied
- Available on internet
- < -1.455: No fibrosis
- > 0.676: significant fibrosis

Limitations:
- Intermediate range
- Inaccurate
- Validation needed

http://nafldscore.com/

Fibrosis: Fibroscan

- Transient elastography
- Studied since 2003
- Measures liver stiffness by wave velocity
- Values range: 2.5 – 75 kPa
- Easy/ Portable (<5min)
- Available > 70 countries

Limiting Factors:
BMI/ Fat/ Ascites: interfere with results
Inflammation/ Congestion/ Cholestasis (falsely high scores)
Operator experience

FDA approved on April 15, 2013

All that’s stiff is not FIBROSIS !!

MR Elastography

- Reliable
- Higher success rates
- Higher Sn/Sp: 80%/ 85%
- Identifies Fat & Fibrosis
- Expensive
- Not readily available

Chen et al; Radiology 2011
Steatosis/ Fibrosis: Radiology

<table>
<thead>
<tr>
<th></th>
<th>Liver Steatosis</th>
<th>Liver Fibrosis</th>
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</thead>
<tbody>
<tr>
<td>Objective &amp; Quantitative</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Failure</td>
<td>&lt; 0.5%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Whole range</td>
<td>Only in high fat range</td>
</tr>
<tr>
<td>Longitudinal Monitoring</td>
<td>Whole range</td>
<td>Possible V/N</td>
</tr>
<tr>
<td>Probe independent</td>
<td>Yes</td>
<td>M probe only</td>
</tr>
<tr>
<td>Cost</td>
<td>$$$</td>
<td>$$$</td>
</tr>
</tbody>
</table>

Invasive Tests: Liver Biopsy

- Gold/ Clinical Standard
- To confirm diagnosis
- To prognosticate:
  - Is there inflammation/ NASH?
  - How much fibrosis?

Disadvantages:
- Invasive
- Risks:
  - Bleeding
  - Injury to adjacent structures
  - Death (0.2%)
  - Sampling errors: Patchy distribution
  - Expensive

Liver Biopsy

- ALT increase in other causes
- Causes Round
- Metabolic syndrome present?
- Yes?
  - Will biopsy change management?
  - Consider liver biopsy for diagnosis
- No?
  - Discussкладерметрическій with patient
  - Make patient aware of potential consequences if biopsy not performed

- No
  - opioid
  - anxiolytic
  - sedative
  - other

- Yes
  - weight loss
  - increased activity

- No
  - diet
  - medication

- Yes
  - no
  - no
  - no
  - no
  - no

- No
  - yes
  - yes
  - yes
  - yes
  - yes
Access to fresh-food grocers and the highest concentration of fast-food outlets, coupled with limited income and extremely poor families with nutritional education.

Other examples of measures that can negate individual and general progress, changes should involve all levels of government, including the extension of well-organized primary care services and community programs. Such services (namely dieticians, exercise physiologists, and psychologists) is also crucial. Additionally, the prioritzation of funding for wider availability of key supportive services (namely dieticians, exercise physiologists, and psychologists) is also crucial. Additionally, the extension of well-organized primary care services and community programs. Such services (namely dieticians, exercise physiologists, and psychologists) is also crucial. Additionally, the extension of well-organized primary care services and community programs.

Screen for CVS and preliminary management (see Surveillance in Cirrhosis for intensive, individualized lifestyle interventions)

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Screen for CVS and preliminary management (see Surveillance in Cirrhosis for intensive, individualized lifestyle interventions)
NAFLD Treatment Targets

- Insulin Resistance
- Oxidative Stress
- Inflammation
- Fibrosis

Life-Style Modifications

<table>
<thead>
<tr>
<th>Modality</th>
<th>Effect</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Diet</td>
<td>Weight Loss: -7-10%</td>
<td>Calorie restriction by 500-750kcal/day</td>
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<tr>
<td></td>
<td>Eliminate or reduce SFA &amp; High Fructose</td>
<td>Fructose better substrate for NAFL → lipogenesis</td>
</tr>
<tr>
<td></td>
<td>Omega-3 Fatty Acids</td>
<td>Improves TG, May reduce NAFL</td>
</tr>
<tr>
<td></td>
<td>Coffee: 2-3 Cups/ day</td>
<td>Decreased fibrosis</td>
</tr>
<tr>
<td>Exercise</td>
<td>Moderate Exercise: Treadmill/ Elliptical/ Pool: 4.5 per week, 3-45min Resistance Training; 3 times/ week, total 45min</td>
<td>Improves insulin resistance, Improves LFT's, Steatosis</td>
</tr>
<tr>
<td></td>
<td>Rigorous results when combined with diet</td>
<td></td>
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</tbody>
</table>

Coffee: Brewing Evidence for Hepatoprotection

<table>
<thead>
<tr>
<th>Coffee Consumption (g/day)</th>
<th>NaFLD</th>
<th>Control</th>
<th>p-value</th>
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<tr>
<td>0</td>
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<td>1.0</td>
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<tr>
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<tr>
<td>20</td>
<td>1.0</td>
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</table>

Scatter plot

Kooby et al. ACG 1992
Kooby et al. Hepatology 2017
Antioxidants

- Oxidative stress is "second hit" in pathogenesis of NAFLD.
- Vitamin E \( \rightarrow \) inhibits TGF \( \beta_1 \) \( \rightarrow \) Anti-inflm \( \rightarrow \) Anti-fibrotic
  - Pediatric NAFLD: Not superior
  - Adults: Dose \( > 400 \) IU is associated with increased mortality
- Other Anti-oxidants in studies:
  - N-acetyl-cysteine
  - Betaine
  - S-Adenosyl methionine

Pioglitazone and Vitamin E PIVENS Trial

![Graph showing improvements in various parameters with Pioglitazone and Vitamin E](image-url)
Pioglitazone and Vitamin E PIVENS Trial

<table>
<thead>
<tr>
<th>Superior histologic improvement</th>
<th>Vitamin E</th>
<th>Pioglitazone</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>Placebo:</td>
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<tr>
<td>Pioglitazone (non-DM, non-</td>
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<tr>
<td>Cirrhotics)</td>
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<tr>
<td>Weight Gain</td>
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<td>Yes</td>
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<tr>
<td>Insulin sensitivity</td>
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<td>Yes</td>
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<tr>
<td>CHF risk</td>
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<td>Yes</td>
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<td>Fracture risk</td>
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<td>Yes</td>
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<tr>
<td>All cause mortality</td>
<td>Mild increase ?</td>
<td>No data</td>
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Sanyal AJ et al; NEJM 2010

Insulin Sensitizers

- Metformin:
  - ↓ Hepatic gluconeogenesis
  - ↓ Intestinal glucose absorption
  - ↓ Serum lipid levels and hepatic FA oxidation
  - Promotes weight loss
  - Human data: no improvement in histology

- TZD’s:
  - Pioglitazone, Rosiglitazone
  - Several studies (Only 3 RCTs)
  - Small samples (10-70 patients)
  - Improved ALT & Histology
  - Irreversible weight gain
  - Long term use: risk of CHF, fractures, Bladder Cancer ?

- Other Insulin Sensitizers:
  - Exenatide, Liraglutide
  - Induces weight loss
  - ↓ hepatic steatosis
  - Ongoing research

NASH: Statins

- No additional hepato-toxicity
- LFT’s although initially elevated will normalize after few months
- Significantly lower CVS risks: 10% vs 30% (P < 0.0001)
### Obeticholic Acid

- OCA: Semi-synthetic bile acid
- FXR agonist
- Insulin sensitizer
- Weight loss
- Filed for FDA approval

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### Obeticholic Acid

- LI: lobular inflammation
- HB: hepatocyte ballooning
- *: Statistically significant

---

### Novel Therapeutics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Human Trials</th>
<th>Outcomes improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incretin Mimetics (Dipeptidyl Peptidase-IV, DPP-IV)</td>
<td>GLP-1 agonist, insulin sensitizer</td>
<td>Yes</td>
<td>ALT, NAS, FIB-4</td>
</tr>
<tr>
<td>Bile Acids: Obeticholic A</td>
<td>FXR agonist, insulin sensitizer</td>
<td>Yes (phase II, 2013)</td>
<td>ALT biomarkers, insulin resistance, WL, less trend</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>TNF/RAβ/IL-1β Anti-inflammatory, fibrotic</td>
<td>Yes</td>
<td>NAS, fibrosis trend</td>
</tr>
<tr>
<td>Lysyl Oxidase Like2-inh (LXL2-i)</td>
<td>Anti-fibrotic, inhibits collagen crosslinking</td>
<td>Ongoing phase II (NASH: S3-4)</td>
<td>Fibrosis trend</td>
</tr>
<tr>
<td>Angiotensin RB (ARB)</td>
<td>Telmisartan Anti-fibrotic, remodelling</td>
<td>Yes</td>
<td>Not significant</td>
</tr>
<tr>
<td>Probiotics (VSL3, Lactobacillus)</td>
<td>Anti-inflammatory, Autophagy + Ulcerative</td>
<td>Yes (4 studies)</td>
<td>ALT, NAS, hepatic lipids</td>
</tr>
<tr>
<td>Exendin 4 + Metformin</td>
<td>Yes</td>
<td>ALT, hepatic lipids</td>
<td></td>
</tr>
<tr>
<td>KD-025</td>
<td>Anti-fibrotic, ROCK2 inhibitor</td>
<td>No</td>
<td>NAS, hepatic lipids</td>
</tr>
<tr>
<td>Carbohydrate Intake Reduction</td>
<td>Insulin sensitizer, weight loss</td>
<td>No</td>
<td>Not significant</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Liraglutide GLP1 R agonist Insulin sensitizer</td>
<td>Yes</td>
<td>ALT, NAS, hepatic lipids</td>
</tr>
<tr>
<td>Carbamazepine, PUFA</td>
<td>Anti-inflammatory, Autophagy + Ulcerative</td>
<td>Yes (few)</td>
<td>NAS, hepatic lipids</td>
</tr>
<tr>
<td>Exendin 4</td>
<td>Byetta Autophagy + Ulcerative</td>
<td>Yes (few)</td>
<td>NAS, hepatic lipids</td>
</tr>
</tbody>
</table>
NAFLD: Transplant

- Current: 9-10% of all LT
- Increasing x last decade
- NASH + HCC: on the rise
- LT evaluation: Thorough
  - CVD risks (12-15% peri-LT)
  - Risk of other cancers
  - BMI > 40 (poor outcomes)

O’Leary et al; Gastro 2008

Summary

- Epidemiology:
  - Increasing in prevalence/ indication for LT
- Diagnosis:
  - Several non-invasive methods being tested: NASH/ Fibrosis
  - Liver Biopsy: Still the “gold standard”
- Treatment:
  - Life-style modifications ***
  - Target agents against specific pathway are cautiously tested
- Transplant related:
  - Thorough evaluation necessary
  - Recurrent/ de novo NAFLD common
  - Graft loss rare but significant morbidity from metabolic syndrome

Current Gaps: Several which need to be addressed soon

Post-Test Questions
Post-test ARS Question 1
Which of the following patients are not at high risk for the development of NAFLD:

1. Patient with Rheumatoid arthritis taking methotrexate for > 10 years
2. Obese woman who lost 100lbs after jejuno-ileal bypass (bariatric surgery)
3. Man with BMI 35 who has DM2 and OSA
4. Young boy with Crohn’s s/p multiple intestinal resections on TPN
5. Middle aged woman with colon cancer in cecum s/p hemicolectomy

Post-test ARS Question 2
CASE
62 year old Caucasian man with Obesity (BMI 45), DM2, Hypertension, Hyperlipidemia, Obstructive Sleep Apnea, and Osteoarthritis of the knees has mildly elevated LFT’s in the past which were attributed to him being on statins. Despite all efforts to lose weight, the patient was able to lose only 2% of his weight due to his limited exercise capacity. Ultrasound demonstrates increased echogenicity of the liver suggestive of fatty liver.

Post-test ARS Question 2
What is the current gold standard to distinguish NAFLD from NASH:

1. Liver biopsy
2. LFT’s
3. Ultrasound
4. MR Spectroscopy
Post-test ARS Question 3

CASE

68 year old Hispanic woman with Metabolic syndrome has new onset ascites and was hospitalized recently for fluid overload. Blood tests show serum albumin of 2.4, platelets of 98k and upper endoscopy which showed grade 2 varices. She underwent a transjugular liver biopsy which shows stage 4 fibrosis.

Post-test ARS Question 3

Given the clinical picture which is consistent with decompensated cirrhosis, how would you screen the patient for hepatocellular carcinoma?

1. MRI abdomen every 2 years
2. CT scan abdomen & pelvis every 2 years
3. Ultrasound abdomen every 6 months
4. Fibroscan every year
5. All the above

Post-test ARS Question 4

CASE

55 year old non-diabetic woman is recently diagnosed with NASH and advanced fibrosis (stage 3) on liver biopsy. You recommend aggressive life-style modifications but the patient was unable to lose > 1% of her body weight over a period of 1 year.
Post-test ARS Question 4
Given the presence of advanced fibrosis in the setting of NASH, which of the following additionally would you recommend in her management that would improve her liver histology?

1. Metformin
2. Orlistat
3. Cholecystectomy
4. Vitamin E
5. Ursodiol

Post-test ARS Question 5
On a scale of 1 to 5, please rate how confident you would be treating a patient with non-alcoholic steatohepatitis:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident

Post-test ARS Question 6
Which of the statements below describes your approach to the evaluation and management of Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis?

1. I do not evaluate patients at risk for NAFLD/NASH or manage this condition, nor do I plan to this year.
2. I did not evaluate patients at risk for NAFLD/NASH or manage this condition, but as a result of attending this course I’m thinking of screening for it and managing patients now.
3. I do evaluate patients at risk for NAFLD/NASH and manage this condition, and this course helped me change my treatment methods.
4. I do evaluate patients at risk for NAFLD/NASH and manage this condition. This course confirmed that I don’t need to change my treatment methods.