Common inflammatory diseases of the liver: hepatitis B, hepatitis C and nonalcoholic fatty liver disease

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Associate Professor of Medicine
Division of Gastroenterology and Hepatology
LEARNING OBJECTIVES

• Overview epidemiology chronic viral hepatitis B and C
• Describe diagnostic approach
• Review goals of antiviral therapy
• Discuss current treatment options and criteria used to select therapy
LEARNING OBJECTIVES

• Define NAFLD and NASH
• Describe magnitude of the problem and natural history
• Review pathogenesis
• Discuss diagnostic approach
• Review current and future management
HEPATITIS B VIRUS (HBV) INFECTION

- HBV blood-borne DNA-virus that infects the liver
- Chronic infection leads to serious liver-related consequences, including liver cancer
- With proper screening, diagnosis, and successful treatment, HBV infection can be controlled although not yet cured
EPIEMIOLOGY HEPATITIS B

Increasing prevalence in some European countries:5,6
- Migration from high endemic countries

Decreasing prevalence in some endemic countries, e.g. Taiwan7
Possible reasons:
- Improved socioeconomic status
- Vaccination
- Effective treatments

EASL CPG HBV. J Hepatol 2017;67:370–98
EPIDEMIOLOGY HBV

• Worldwide ≈260 million chronic HBsAg

• US ~1 to 2 million persons chronic HBV
  – Asian & Pacific Islanders >50% US patients with HBV
  – Overall ~65% unaware HBV infection

• Worldwide HBV infection is the most common cause for hepatocellular carcinoma

# INTERPRETATION SCREENING TESTS HBV INFECTION

<table>
<thead>
<tr>
<th>Screening Test Results</th>
<th>Interpretation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBsAg</strong></td>
<td><strong>Anti-HBc</strong></td>
<td><strong>Anti-HBs</strong></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>-</td>
<td>+</td>
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</tr>
</tbody>
</table>

## NEW NOMENCLATURE CHRONIC PHASES

<table>
<thead>
<tr>
<th></th>
<th>HBeAg positive</th>
<th>HBeAg negative</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1</strong></td>
<td>Chronic HBV infection</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Phase 2</strong></td>
<td>Chronic hepatitis B</td>
<td>High/intermediate</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td>Chronic HBV infection</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Phase 4</strong></td>
<td>Chronic hepatitis B</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Phase 5</strong></td>
<td>Resolved HBV infection</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

### HBsAg
- **High**
- **High/intermediate**
- **Low**
- **Intermediate**
- **Negative**

### HBeAg
- **Positive**
- **Positive**
- **Negative**
- **Negative**
- **Negative**

### HBV DNA
- **>10^7 IU/mL**
- **10^4–10^7 IU/mL**
- **<2,000 IU/mL**
- **>2,000 IU/mL**
- **<10 IU/mL**

### ALT
- **Normal**
- **Elevated**
- **Normal**
- **Elevated**
- **Normal**

### Liver disease
- **None/minimal**
- **Moderate/severe**
- **None**
- **Moderate/severe**
- **None**

### Old terminology
- **Immune tolerant**
- **Immune reactive HBeAg positive**
- **Inactive carrier**
- **HBeAg negative chronic hepatitis**
- **HBsAg negative / anti-HBc positive**

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GOALS OF THERAPY

• Improve survival and quality of life by preventing disease progression and HCC development
• Prevent mother-to-child transmission
• Prevent hepatitis B reactivation
• Prevent/treat HBV-associated extrahepatic manifestations

EASL CPG HBV. J Hepatol 2017;67:370–98
## TREATMENT ENDPOINTS

### Recommendations

<table>
<thead>
<tr>
<th>Endpoint Type</th>
<th>Description</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main endpoint</strong></td>
<td>Induction of long-term suppression of HBV DNA</td>
<td>I 1</td>
</tr>
<tr>
<td><strong>Valuable endpoint</strong></td>
<td>Induction of HBeAg loss (± anti-HBe seroconversion) in HBeAg-positive patients with chronic hepatitis B</td>
<td>II-1 1</td>
</tr>
<tr>
<td><strong>Additional endpoint</strong></td>
<td>ALT normalization (biochemical response)</td>
<td>II-1 1</td>
</tr>
<tr>
<td><strong>Optimal endpoint</strong></td>
<td>HBsAg loss (± anti-HBs seroconversion)</td>
<td>II-1 1</td>
</tr>
</tbody>
</table>
## INDICATIONS FOR TREATMENT

### Recommendations

#### Should be treated
- Patients with HBeAg-positive or -negative chronic hepatitis B
- Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level
- Patients with HBV DNA >20,000 IU/mL and ALT >2x ULN, regardless of severity of histological lesions

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should be treated</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>I. Patients with HBeAg-positive or -negative chronic hepatitis B</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>II-2. Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>III. Patients with HBV DNA &gt;20,000 IU/mL and ALT &gt;2x ULN, regardless of severity of histological lesions</td>
<td>III</td>
<td>1</td>
</tr>
</tbody>
</table>

#### May be treated
- Patients with HBeAg-positive chronic HBV infection >30 years old, regardless of severity of liver histological lesions

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>May be treated</td>
<td>III</td>
<td>2</td>
</tr>
</tbody>
</table>

#### Can be treated
- Patients with HBeAg-positive or -negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be treated</td>
<td>III</td>
<td>2</td>
</tr>
</tbody>
</table>

EASL CPG HBV. J Hepatol 2017;67:370–98
THERAPY FOR TREATMENT-NAÏVE PATIENTS

• Long-term administration of potent nucleoside analogues with high barrier to resistance is treatment of choice

• FDA-approved: entecavir (ETV), tenofovir disoproxil fumarate (TDF) & tenofovir alafenamide (TAF)

• In specific clinical scenarios ETV or TAF may be more appropriate choices than TDF

EASL CPG HBV. J Hepatol 2017;67:370–98
HBV AND HCV CO-INFECTION

• HCV co-infection accelerates liver disease progression and increases risk of HCC in patients with chronic HBV infection

• All patients with chronic HBV infection should be screened for HCV and other blood-borne viruses (HIV and HDV)
## HBV AND HCV CO-INFECTION

### Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of HCV with DAAs may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment should receive NA treatment</td>
<td>II</td>
<td>1</td>
</tr>
<tr>
<td>HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until 12 weeks after completion of DAA treatment, and monitored closely</td>
<td>II-2</td>
<td>2</td>
</tr>
<tr>
<td>HBsAg-negative, anti-HBc-positive patients undergoing DAA therapy should be monitored and tested for HBV reactivation in case of ALT elevation</td>
<td>II</td>
<td>1</td>
</tr>
</tbody>
</table>
ACUTE HBV INFECTION

Recommendations

More than 95% of adults with acute HBV hepatitis do not require specific treatment

<table>
<thead>
<tr>
<th>II-2</th>
<th>1</th>
</tr>
</thead>
</table>

Only patients with severe acute hepatitis B, characterized by coagulopathy or protracted course, should be treated with NAs and considered for liver transplantation

| II-2 | 1 |
# HBV AND IMMUNOSUPPRESSION

## Recommendations

<table>
<thead>
<tr>
<th>All candidates for chemotherapy and immunosuppressive therapy <strong>should be tested</strong> for HBV markers prior to immunosuppression</th>
<th>I</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HBsAg-positive patients should receive ETV, TDF, or TAF as treatment or prophylaxis</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>HBsAg-negative, anti-HBc-positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation</td>
<td>II-2</td>
<td>1</td>
</tr>
</tbody>
</table>
FUTURE TREATMENT HBV

• Several novel direct-acting antivirals and immunotherapeutic agents are in preclinical and early clinical development

• Combinations of antiviral and immune modulatory therapy, targeting multiple steps in the HBV lifecycle, will likely be needed to achieve an HBV ‘cure’
HEPATITIS C VIRUS (HCV) INFECTION

- HCV blood-borne RNA-virus that infects liver
- Chronic infection can lead to serious liver-related consequences (cirrhosis, HCC)
- With proper screening, diagnosis, and successful treatment, **HCV infection can be cured**
HEPATITIS C GLOBAL EPIDEMIOLOGY

An estimated 70 million (56 million – 90 million) individuals are infected with HCV (viremic), a prevalence of 1% (0.8%-1.2%) in 2016.

In 2015, 500K patients were treated and cured with DAAs.

Source: Polaris Observatory (http://www.polarisobservatory.com/)
HEPATITIS C IN THE UNITED STATES

• Prevalence HCV viremia ~1%
• Viremic population ~3 million persons
• Genotype distribution:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Percentage</th>
<th>Count</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>46%</td>
<td>3</td>
<td>9%</td>
</tr>
<tr>
<td>1b</td>
<td>26%</td>
<td>4</td>
<td>6%</td>
</tr>
<tr>
<td>2</td>
<td>11%</td>
<td>6</td>
<td>1%</td>
</tr>
</tbody>
</table>
HEPATITIS C RISK FACTORS UNITED STATES

- Injection Drug Use: 46.7%
- HCV-Positive Sex Partner*: 29.3%
- Health Care Worker & Blood Exposure: 3.7%
- Multiple Sex Partners: 1.5%
- Blood Transfusion: 1.9%
- HCV-Positive Household Contact: 3.3%
- Aggregate Risk Category**: 3.3%
- No Risk Factor Identified: 10.7%
HEPATITIS C IN THE UNITED STATES

- HCV is approximately 4 times as prevalent as HIV and HBV in the United States
- A 2011 study estimated that as many as 5.2 million persons are living with HCV in the United States
CDC TESTING RECOMMENDATIONS

• Hepatitis C screening at least once in a lifetime for all adults aged ≥18 years
• Hepatitis C screening for all pregnant women during each pregnancy
• Regardless of age or setting prevalence, all persons with risk factors should be tested for hepatitis C, with periodic testing while risk factors persist

HEPATITIS C IMPACT ON LIFE EXPECTANCY

HEPATITIS C DIAGNOSIS

HCV Antibody

Nonreactive

Reactive

HCV RNA

Not Detected

Detected

Current HCV Infection

No Current HCV Infection

No HCV Antibody Detected

Stop

Link to Care

Additional Testing as Appropriate
HEPATITIS C IN THE UNITED STATES
DISTRIBUTION OF LIVER FIBROSIS (FIB-4, 2016)

www.mappinghepc.com/maps
HEPATITIS C TREATMENT GOALS

Primary Goal

Eradicate HCV infection

Secondary Goal

Slow disease progression
Improve histology
Reduce risk of HCC
HEPATITIS C
BENEFITS OF THERAPY

- HALT-C Trial: multicenter study 1145 patients with advanced liver fibrosis treated with PEG-IFN/RBV
- Sustained viral response (SVR) significantly reduced HCV-associated complications and mortality

HEPATITIS C IN THE UNITED STATES
PROPORTION OF PERSONS DIAGNOSED AND TREATED

75.0%

25.0%

10%-25%

75%-90%

Diagnosed  Undiagnosed

Treated  Untreated
HEPATITIS C IN THE UNITED STATES

PROPORTION HCV RNA (+) PATIENTS STARTED DAA

Percentage of HCV RNA+ individuals treated in 2016

24.1%

19.2%
DIRECT ACTING ANTIVIRALS (DAA)

**NS3/4A Protease Inhibitors (PI)**
- High potency
- Multi-genotypic coverage
- Intermediate to high barrier to resistance

**NS3/4A Protease Inhibitors (PI)**
- Intermediate potency
- Pan-genotypic coverage
- High barrier to resistance

**NS5A Inhibitors**
- High potency
- Multi-genotypic coverage
- Low to intermediate barrier to resistance

**NS5B Nucleoside Inhibitors (NI)**
- Intermediate potency
- Limited-genotypic coverage
- Low barrier to resistance

EVOLUTION OF ANTIVIRAL THERAPY

Discovery of HCV (Chiron) 1989
Approval Ribavirin 1992
Approval pegIFN 1998
Genotype-Specific RGT 2001
Approval Telaprevir/Boceprevir 2005
Approval Ledipasvir/Sofosbuvir PrOD 2011
Approval Grazoprevir/Elbasvir 2013
Approval Simeprevir/Sofosbuvir 2014
Approval Daclatasvir PrO 2015
Approval Sof/Vel/Voxelaprevir 2018

SVR: 6% 12% 20% 40% 54% 65–75% > 90%

Courtesy: Hugo E. Vargas, MD, Mayo Clinic
FACTORS THAT IMPACT DAA SELECTION AND TREATMENT DURATION

• Viral genotype
• Presence/absence liver cirrhosis
  – Compensated vs. decompensated
• Prior treatment experience
  – NS5A resistance, RAVs in prior non-responders
• Renal function (CKD stage 4 or 5)
• Drug-drug interactions
• Solid organ transplant status
CONCLUSIONS

• **5 million** persons living with HBV or HCV in United States
• **65-75%** infected individuals not aware of their status
• HBV is “treatable”, although not yet "curable", long-term viral suppression is common
• New antiviral and immune modulatory therapies in development
• **HCV is curable**
• Newer DAA regimens:
  – Treat all genotypes (pangenotypic)
  – Shorter duration treatment (8-12 weeks in most cases)
NON-ALCOHOLIC FATTY LIVER DISEASE

• Initial histologic description by Dr. J. Ludwig and colleagues at Mayo Clinic in 1980
• Histopathologic injury similar to that seen in alcohol liver disease among patients without significant alcohol intake = ”nonalcoholic fatty liver disease” (NAFLD)
DEFINITIONS

NAFLD
- Excessive hepatic fat accumulation
- Steatosis in >5% of hepatocytes
- Exclusion of secondary causes and ALD

NAFL
- Pure steatosis
- Steatosis and mild lobular inflammation

NASH
- Early F0/F1 fibrosis
- Fibrotic F2 to F3 fibrosis
- Cirrhotic F4 fibrosis

HCC

Definitive diagnosis of NASH requires a liver biopsy
NAFLD EPIDEMIOLOGY
GENERAL POPULATION

• NAFLD most common cause liver disease worldwide

• Global prevalence 25% adult population
  – Middle East 32%
  – South America 30%
  – United States 30%
  – Africa 14%

• NASH among NAFLD patients: 25-30%

• NASH prevalence 1.5%-6.5% adults worldwide
NAFLD PREVALENCE UNITED STATES
NAFLD EPIDEMIOLOGY
HIGH RISK POPULATION

• Obesity (BMI >30 kg/m²)
  – NAFLD affects 50% obese persons
  – NAFLD affects 95% undergoing bariatric surgery
• Type 2 DM 25%-60%
• Dyslipidemia 70%
• Hypertension 40%
• Metabolic syndrome 40%

Hepatology 2016;64:73
Hepatology 2018;67:328
PROJECTED OBESITY IN ADULTS IN THE US

BMI >30 kg/m²

BMI >35 kg/m²

N Engl J Med 2019;381:2440
NAFLD ECONOMIC BURDEN

• United States: 64 million persons NAFLD → annual medical cost $100 billion ($1,600/person)

• NASH with fibrosis: 3 to 4 million persons → annual cost $10 - $15 billion
UNITED STATES PREVALENCE NAFLD ADJUSTED BY AGE AND SEX
NAFLD CURRENT AND FUTURE BURDEN OF DISEASE IN THE UNITED STATES

![Graph showing the total prevalent NAFLD/NASH cases in the US from 2015 to 2030. The graph indicates a steady increase in NAFLD cases and a slight decrease in NASH cases over this period.](image-url)
NAFLD CURRENT AND FUTURE BURDEN OF DISEASE IN THE UNITED STATES
NAFLD PROGNOSIS

• Strong association between NAFLD and cardio-metabolic complications resulting increased cardiovascular morbidity and mortality

• Main causes of mortality: cardiovascular disease, non-liver malignancies and liver-related mortality with increased risk of HCC

• Stage of liver fibrosis most important predictor cardiovascular and liver-related complications and death
NASH PATHOGENESIS

- Normal hepatocyte
- Fatty hepatocyte
- Fatty and injured hepatocyte
- Apoptotic hepatocyte

Adipose tissue → Gut and microbiome

Metabolic stress → Ballooned

Lipotoxicity

Cell signals

Repair-related cells:
- Immune cells
- Activated sinusoidal endothelium
- Myofibroblastic stellate cell
- Reactive ductal cells

Wound-healing responses:
- Inflammation
- Vascular remodeling
- Fibrogenesis
- Accumulation of immature liver epithelial cells

N Engl J Med 2017;377:2063
PATHOPHYSIOLOGY

GENETICS

• Specific SNP influence development NAFLD & NASH
  – Patatin-like phospholipase 3 (PNPLA3) or adiponutrin single nucleotide polymorphism confers increased risk NASH and liver fibrosis and is more prevalent among Hispanics

Hepatology 2011;53:1883-1894
DIAGNOSIS

CLINICAL QUESTIONS

• Does this patient have NAFLD or another liver disease?
• If NAFLD, does the patient have NASH?
• If NASH, does the patient have advanced fibrosis?
# NAFLD Imaging Diagnosis

Comparison of ultrasound, computed tomography, and MRI for detection and evaluation of hepatic steatosis

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>• Widely accessible&lt;br&gt;• Inexpensive</td>
<td>• Suboptimal sensitivity/specificity for mild steatosis&lt;br&gt;• Operator dependent&lt;br&gt;• Qualitative</td>
</tr>
<tr>
<td>CT</td>
<td>• High sensitivity for moderate to severe steatosis</td>
<td>• Suboptimal sensitivity/specificity for mild steatosis&lt;br&gt;• Radiation risks</td>
</tr>
<tr>
<td>MRI</td>
<td>• Best sensitivity and sensitivity for steatosis (even mild steatosis)&lt;br&gt;• May be superior to biopsy specimen in terms of estimating total hepatic fat&lt;br&gt;• Can be used to follow patients longitudinally with treatment</td>
<td>• Expensive&lt;br&gt;• Limited availability as a screening tool</td>
</tr>
</tbody>
</table>
NAFLD/NASH DIAGNOSTIC EVALUATION

<table>
<thead>
<tr>
<th>Least invasive</th>
<th>Fibrosis</th>
<th>NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fibroscan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NAFLD Fibrosis store/BARD</td>
<td>CK18 NASHTest/FibroMax</td>
</tr>
<tr>
<td></td>
<td>Fibrotest/ELF score</td>
<td>Contrast USS</td>
</tr>
<tr>
<td>Most invasive</td>
<td>Liver biopsy</td>
<td>Liver biopsy</td>
</tr>
</tbody>
</table>
NAFLD
DIAGNOSTIC IMAGING FIBROSIS

- Technological advances have allowed development of non-invasive assessment of liver elasticity as surrogate of fibrosis
  - Transient elastography (FibroScan®)
  - MR elastography
  - Acoustic radiation force impulse (ARFI)
VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY (FIBROSCAN®)
TABLE 4
Fibrosis stages and proposed transient elastography cutoffs

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Cutoff (kPa)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F ≥2</td>
<td>5.35–7.4</td>
<td>87.5</td>
<td>78.4</td>
</tr>
<tr>
<td>F ≥3</td>
<td>8.0–12.85</td>
<td>93.7</td>
<td>91.1</td>
</tr>
<tr>
<td>F ≥4</td>
<td>10.3–17.5</td>
<td>96.2</td>
<td>92.2</td>
</tr>
</tbody>
</table>

Suspected NAFLD (Hepatic steatosis on imaging ± elevated serum ALT levels)

Evaluate alcohol consumption

Confirmation of NAFLD

Exclude alternate causes of ↑ALT levels

Risk stratification for liver-related outcomes

Low-risk profile
- BMI <29.9
- Age <40 years
- No T2DM or metabolic syndrome features
- Noninvasive fibrosis estimation‡:
  - FIB-4 <1.30
  - APRI <0.5
  - NFS <−1.455
  - Fibroscan® <5 kPa*

Follow and reassess patient as risk factors evolve

Intermediate-risk profile
- BMI >29.9
- Age >40 years
- Multiple features of the metabolic syndrome
- Noninvasive fibrosis estimation‡:
  - FIB-4 1.30–2.67
  - APRI 0.5–1.5
  - NFS −1.455–0.675
  - Fibroscan® 6–11 kPa*

Consider liver biopsy

High-risk profile
- AST level >AST level
- Platelets <150,000
- Noninvasive fibrosis estimation‡:
  - FIB-4 >2.67
  - APRI >1.5
  - NFS >0.675
  - Fibroscan® >11 kPa*

Consider liver biopsy or confirmatory testing for cirrhosis such as magnetic resonance elastography
WHAT I WANT TO KNOW FROM A LIVER BIOPSY?

• Does the patient have NAFL or NASH?
• Is there an alternative diagnosis?
• How much fibrosis is there (F0-F4)?
# NAFLD HISTOLOGY SCORING SYSTEMS

<table>
<thead>
<tr>
<th>NAS (NASH CRN)</th>
<th>SAF (FLIP consortium)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>Steatosis</td>
</tr>
<tr>
<td>Ballooning</td>
<td>Activity</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Ballooning (0–2)</td>
</tr>
<tr>
<td></td>
<td>Inflammation (0–2)</td>
</tr>
<tr>
<td></td>
<td>Fibrosis</td>
</tr>
<tr>
<td>NAS</td>
<td>SAF</td>
</tr>
</tbody>
</table>

0–8 | S0–S3 0–4 A0–A4 F0–F4
# NASH AND LIFESTYLE MODIFICATIONS

## Table 1. Lifestyle Modifications to Mitigate Nonalcoholic Steatohepatitis.*

<table>
<thead>
<tr>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lose 7% of body weight if overweight or obese</td>
</tr>
<tr>
<td>Limit consumption of fructose-enriched beverages</td>
</tr>
<tr>
<td>Limit consumption of alcohol (≤1 drink/day for women and ≤2 drinks/day for men)</td>
</tr>
<tr>
<td>Drink two or more cups of caffeinated coffee daily</td>
</tr>
</tbody>
</table>

*N Engl J Med 2017;377:2063*
CURRENT MANAGEMENT NAFLD/NASH

• Weight loss 7-10% and moderate caloric restriction coupled with regular exercise are most beneficial
• Pioglitazone or vitamin E in biopsy-proven NASH
• Bariatric surgery in selected patients can result in histologic improvement
BARIATRIC SURGERY AND NAFLD/NASH

• NAFLD present 24%-98% obese patients
• Meta-analysis 15 studies evaluating histologic changes after bariatric surgery:
  – 92% improved/resolved steatosis
  – 82% improved/resolved NASH
  – 66% improved/resolved fibrosis

Hepatic Medicine: Evidence & Research 2014:6 103-112
Clin Gastroenterol Hepatol 2008;6:1396-1402
MECHANISM OF ACTION TREATMENT NAFLD/NASH
# NAFLD Treatment

## Histologic Outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Steatosis</th>
<th>Reduction NAS</th>
<th>NASH resolution</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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CONCLUSIONS

• NAFLD growing public health problem closely tied to obesity epidemic
• NAFLD associated with increased cardiovascular morbidity and mortality
• Liver biopsy currently best tool to stage NAFLD and select patients with NASH and fibrosis at increased risk for poor clinical outcomes
CONCLUSIONS

• Lifestyle changes are mainstay of therapy
• Bariatric surgery in select patients improves histology
• Currently limited pharmacologic intervention, although multiple pharmaceuticals are in clinical trials