DISCLOSURE

Commercial Interest

• Arrowhead Pharmaceuticals - Research Grant, Travel/Research Support
• Genfit/Covance - Travel Support (as Sub-Investigator)

Sub-Investigator

Genfit, Intercept Pharmaceuticals, Allergan, Gilead, Allakos, Pharmicell, Sequana Medical, Mallinckrodt Pharmaceuticals, Conatus, Dova Pharmaceuticals

Investigational and off-label use of therapies will be discussed during this presentation
LiverTox provides up-to-date, unbiased and easily accessed information on the diagnosis, cause, frequency, clinical patterns and management of liver injury attributable to prescription and nonprescription medications and selected herbal and dietary supplements. The LiverTox site is meant as a resource for both physicians and patients as well as for clinical academicians and researchers who specialize in idiosyncratic drug induced hepatotoxicity.

Information on specific medications or supplements can be found by entering its name in the “Search this book” box shown above or by browsing the list of agents by its first letter using the alphabetic list shown below.

LiverTox is produced by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and is copyright free. It is requested that use of LiverTox data in publications be given appropriate acknowledgement.

For more information, see About LiverTox

LiverTox Database Updated: 06 Feb 2020

Drug Records
DILI TYPES AND SCORING SYSTEMS

• Types: Hepatocellular (R>5), Cholestatic (<2), And Mixed (2-5)  \( R \text{ (Ratio)} = \frac{\text{ALT}}{\text{Alk Phos}} \)

• HY’s Law: Patients with DILI with bilirubin >2 and ALT >3x ULN have a 10% mortality even if the offending drug is discontinued

• In 83 deaths (Hayashi et al) MELD > 19 (AUROC 0.83): better predictor of acute DILI death <26 weeks. Hy’s Law AUROC 0.60.

• CIOMS/RUCAM SCALE (Roussel Uclaf Causality Assessment Method)
  • Time to onset of the injury following start of the drug
  • Subsequent course of the injury after stopping the drug
  • Specific risk factors (age, alcohol use, pregnancy)
  • Use of other medications with a potential for liver injury
  • Exclusion of other causes of liver disease
  • Known potential for hepatotoxicity of the implicated drug
  • Response to re-challenge
  • Hepatotoxicity Scoring: ≤3 = Unlikely; 4-5 = Possible; 6-8 = Probable; >8: Highly probable

<table>
<thead>
<tr>
<th>Histologic Pattern</th>
<th>Description</th>
<th>Example Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis</td>
<td>Predominantly lobular inflammation and damage that overshadows portal inflammation. No fibrosis.</td>
<td>Fluoroquinolones; nitrofurantoin and methyldopa (acute autoimmune)</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>Predominantly portal inflammation with varying degrees of lobular inflammation. No cholestasis. Variable degrees of portal fibrosis.</td>
<td>Nitrofurantoin, methyldopa</td>
</tr>
<tr>
<td>Acute cholestasis</td>
<td>Deposition of bile in either a hepatocellular or canalicular pattern with minimal inflammation.</td>
<td>Estrogens, androgenic steroids</td>
</tr>
<tr>
<td>Chronic cholestasis</td>
<td>Bile deposition with evidence of duct injury, such as ductular proliferation or ductopenia.</td>
<td>Floxuridine</td>
</tr>
<tr>
<td>Cholestatic hepatitis</td>
<td>A combination of hepatitis and cholestatic patterns.</td>
<td>Amoxicillin-clavulanate, fluoroquinolones, Phenytoin</td>
</tr>
<tr>
<td>Granulomatous inflammation</td>
<td>Nonnecrotizing epithelioid granulomas.</td>
<td>Phenobarbital, Methotrexate, tamoxifen</td>
</tr>
<tr>
<td>Macroversicular steatosis</td>
<td>Variable degrees of accumulation of large fat droplets with peripheral displacement of the nucleus without significant inflammation or cholestasis or alternate pattern.</td>
<td>Valproic acid, tetracycline</td>
</tr>
<tr>
<td>Microvesicular steatosis</td>
<td>Diffuse hepatocyte accumulation of small fat droplets maintaining a central placement of the nucleus without significant inflammation or cholestasis or alternate pattern.</td>
<td>Amiodarone, tamoxifen, methotrexane</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>Steatosis with hepatocyte ballooning, variable degrees of inflammation, and fibrosis.</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Zonal necrosis</td>
<td>Coagulative hepatocyte necrosis within 1 of the 3 zones of the liver acinar unit (zone 3 is most common).</td>
<td>Isoniazid, nitrofurantoin, methyldopa</td>
</tr>
<tr>
<td>Massive or submassive necrosis</td>
<td>Confluent multiacininar necrosis with variable inflammation.</td>
<td>Cidofovir, Ciclosporin, Mitomycin, Doxorubicin, Vinblastine, Methotrexate, Tamoxifen, Raltrex, Lorlatin (no specific associations)</td>
</tr>
<tr>
<td>Sinusoidal obstruction</td>
<td>Sinusoidal dilatation and congestion, central venule occlusions, perisinusoidal fibrosis.</td>
<td>Chemotheaputic agents, bone marrow transplant regimen, No specific associations</td>
</tr>
<tr>
<td>syndrome/veno-occlusive disease</td>
<td>A combination of 2 or more other patterns or significant change that does not qualify for another pattern.</td>
<td>No specific associations</td>
</tr>
<tr>
<td>Mixed or unclassifiable injury</td>
<td>Minor changes such as minimal inflammation or steatosis that do not qualify as normal or for another pattern.</td>
<td>No specific associations</td>
</tr>
<tr>
<td>Minimal nonspecific changes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intrinsic Drug Induced Liver Injury
Acetaminophen Hepatotoxicity
Zone 3 perivenular coagulative necrosis
Zone 1 portal viable hepatocytes
No inflammation

50% - US Acute Liver Failure Cases
20 billion doses sold, $87 million to treat complications
Very high INR, Bilirubin <5
Treatment: N-acetyl-cysteine (1977)
IDIOSYNCRATIC DILI

• 60,000 Cases/Year In US
• Incidence: 10 – 20 / 100,000
• 13-16% Of Acute Liver Failure
• Most Cases: Mild, Self Limited
• Risk Factors:
  • Children At Lower Risk
  • Women At Higher Risk To Progress To Acute Liver Failure
  • 77% Of All Cases Associated With Drug Doses > 50 mg Daily
  • Genetics - Poorly Understood

K Fisher et al. Arch Pathol Lab Med. 2015;139:876-887
Gastroenterology 2013; 144:1419
DILI
Antibiotics 40%
Herbal And Dietary Supplements 20%

Example associated drugs:
Amoxicillin-Clavulanate, Trimethoprim-Sulfamethoxazole, Ciprofloxacin,
Nitrofurantoin, Isoniazid, Tyrosine Kinase Inhibitors, TNF-alpha Inhibitors, Checkpoint inhibitors

Types:
Metabolic and Hypersensitivity
DRUG INDUCED AUTOIMMUNE HEPATITIS

Nitrofurantoin

Acute Form: 1-2 Weeks after Treatment
0.3 Cases Per 100,000 Prescriptions

Chronic Form: Months to Years After Treatment
1 Per 1500 Persons Exposed

• Nitrofurantoin, Minocycline, Methyldopa, Hydralazine
• +ANA, +SMA, IgG >1.1x ULN
• Marked portal and lobular inflammation; predominantly plasma cells with severe interface hepatitis
IMMUNE MEDIATED DILI

- Delayed onset attack – typical of adaptive T-cell response
- Rapid toxicity on re-challenge – typical of memory cells
- HLA associations with particular drugs
- Poorly defined genetic and non-genetic factors
Flucloxacillin

- 1 in 10,000 develop jaundice
- Strong association between HLA risk allele (HLA B*57:01) and DILI
- In spite of this, less than 1 in 500 individuals with this allele will develop DILI

**IMMUNE MEDIATED DILI**

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA</th>
<th>Population</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti TB drugs (isoniazid, rifampicin, pyrazinamide)</td>
<td>DQA1<em>01:02, DQB1</em>02:01</td>
<td>Indian</td>
<td>0.2</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>A<em>02:01, A</em>30:02, B<em>18:01, DQB1</em>04:02,</td>
<td>Caucasian (NW Europe)</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>DRB1<em>07, DRB1</em>15:01-DQB1*06:02</td>
<td>Caucasian (Europe)</td>
<td>2.3–10</td>
</tr>
<tr>
<td>Clometacin</td>
<td>B*08</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>B<em>57:01, DRB1</em>07:01-DQB1<em>03:03, DRB1</em>15</td>
<td>Caucasian (N Europe)</td>
<td>7.0</td>
</tr>
<tr>
<td>Flupiridine</td>
<td>DRB1<em>16:01-DQB1</em>05:02</td>
<td>Caucasian (Europe)</td>
<td>18.7</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>DQB1<em>02:02, DRB1</em>07:01-DQA1*02:01</td>
<td>Caucasian (Europe)</td>
<td>2.6–9</td>
</tr>
<tr>
<td>Lumarcoxicil</td>
<td>DRB1<em>15:01-DQA1</em>01:02-DRB1<em>06:02-DRB5</em>01:01</td>
<td>Caucasian (N Europe)</td>
<td>5.0</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>B<em>58:01, DRB1</em>01, DRB1*01:02</td>
<td>South African, Caucasian (Europe)</td>
<td>-</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>A<em>33:03, B</em>44:03, Cw*14:03</td>
<td>Japanese</td>
<td>13</td>
</tr>
<tr>
<td>Ticlopidine (mercapto-propionylglycine)</td>
<td>A<em>33 B</em>44 DR6</td>
<td>Japanese</td>
<td>6.7</td>
</tr>
<tr>
<td>Tiopronine (mercapto-propionylglycine)</td>
<td></td>
<td>Japanese</td>
<td>7.3</td>
</tr>
<tr>
<td>Ximelagatran</td>
<td>DRB1<em>07:01-DQA1</em>02:01</td>
<td>Caucasian (N Europe)</td>
<td>4.4</td>
</tr>
</tbody>
</table>
CURRENT FDA REQUIRED GENETIC TESTING

• Carbamazepine Related Steven Johnson Syndrome/TENS
  • Testing For HLA-B*15:02 Required By FDA In All Asians
    • Chung et al. 100% positive for allele in 44 cases in Han Chinese SJS/TENS (1996-2003)
    • OR: 1357. In Taiwan, 7.7% PPV, 100% NPV, 98.3% Sensitivity, 97% Specificity
    • NNT: 407 people need to be screened to prevent 1 case

• Abacavir Antiretroviral Hypersensitivity
  • HLA-B*57:01 Testing Required By FDA (All Ethnicities)
    • Mallal et al. 5.6% allele prevalence in 1956 patients from 19 countries
    • NPV 100%, PPV 47.9%
    • Immunologically confirmed hypersensitivity reaction 2.7% (control) vs 0% (screening)

• Cholestatic hepatitis
• Portal infiltrate with lymphocytes, eosinophils, plasma cells
• Biliary epithelial damage, canalicular bile plugs, bile laden macrophages

Amoxicillin/Clavulanate
• DILI – 1.7 PER 10,000 RX
• Time to onset: Average 3 weeks
• Fever, Jaundice, GI symptoms; Rash, Eosinophilia
• More common in men, elderly, multiple courses
• Can be hepatocellular, cholestatic, or both
• Most patients recover in 4-6 months

LiverTox; K Fisher et al. Arch Pathol Lab Med. 2015;139:876-887
Amiodarone

- Damage to lipid bilayer, disturbance of lysosomal and mitochondrial function
- Steatohepatitis
- Ballooned hepatocytes and Mallory Denk bodies
- Enzyme elevations 15-50% of patients
- Clinically apparent liver injury in 1% annually

Methotrexate

- Steatosis and lobular inflammation
- 5% have liver enzyme elevations >2x ULN
- 30% have histologic abnormalities and up to 20% have fibrosis after 1-10 gm cumulative use
- Cirrhosis can occur in >20% after 5-10 yrs
- Clinically apparent disease and fibrosis rare with modern regimens (5-15 mg weekly dosing)
- Folate decreases liver abnormalities
- Monitor closely.
- Hold if AST/ALT 2x ULN, consider liver biopsy/stopping if persistent enzyme elevations (ACR guidelines). AAD guidelines: Consider biopsy for cumulative dose 1-1.5 gm (high risk) or 3.5-4 gm (low risk patients)
TNF-ALPHA INHIBITORS

- Monoclonal antibody to TNF-alpha
- Indication: RA, AS, Psoriatic arthritis, severe psoriasis, Crohn’s, ulcerative colitis
- DILI - Most frequent: Infliximab
- DILI - Least frequent: Etanercept
- Four types of hepatic injury
  - Hepatocellular injury (2-5 weeks)
  - Autoimmune injury (6 months)
  - Cholestatic injury (few days to 24 weeks)
  - Reactivation of chronic hepatitis B

LiverTox; Rossi RE et al. World J Gastroenterol. 2014 Dec 14;20(46):17352-9
CHECKPOINT INHIBITORS

- CTLA-4 blockade: Ipilimumab
- PD-1 inhibition: Nivolumab, Pembrolizumab
- PD-L1 inhibition: Atezolizumab
- Antibody inhibition of receptors leads to activation and proliferation of T cells
- Adverse reactions (up to 50%): Enterocolitis, hepatitis, other systemic inflammatory conditions
- Hepatitis: Acute, immune mediated
  - 10%: Mild-moderate enzyme elevations
  - 0.5-1.5%: ALT>5x ULN (after 2-6 cycles)
  - Treatment Grade 2-3: Prednisone 1-2 mg/kg/day, Mycophenolate Mofetil 500-1000 mg BID if needed

LiverTox; Reddy HG et al. Clin Transl Gastroenterol. 2018 Sep;9(9):180
NAFLD

- Most common liver disease worldwide
- Incidence: 28 per 1,000 person years
- Global prevalence: 25% adult population
- Discovery often incidental (e.g. LFT’s, imaging)
- Hepatic steatosis (imaging or histology) > 5% liver parenchyma
  - NAFL = Simple steatosis
  - NASH = Steatosis + Hepatocellular injury ± Fibrosis
  - Exclude secondary causes
    - Significant alcohol use
    - Long term steatogenic medications
    - HCV Genotype 3, Wilson’s, Starvation, TPN, AFLP, HELLP, Inborn errors of metabolism
NAFLD Risk Factors

• Obesity 50%
  • >95% in those undergoing bariatric surgery
• Type 2 DM (25-60%)
• Dyslipidemia (70%)
• Metabolic syndrome (40%)
• PCOS

Other conditions

• Hypothyroidism, OSA, Hypopituitarism, Hypogonadism
NAFLD
- Excessive hepatic fat accumulation with IR
- Steatosis in >5% of hepatocytes
- Exclusion of secondary causes and alcoholic fatty liver disease

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

EASL CPG NAFLD. J Hepatology 2016
Insulin resistance promotes increase in free fatty acids to liver which can trigger hepatic lipotoxicity

Genetic factors such as PNPLA3 variants can affect intrahepatic TG content and insulin resistance

Pathogenesis of NAFLD probably involves inter-organ crosstalk: adipose tissue, pancreas, gut, and liver
NORMAL LIVER CHEMISTRIES (ACG GUIDELINES 2017)

• A true healthy normal ALT level in prospectively studied populations without identifiable risk factors for liver disease ranges from 29 to 33 IU/l for males and 19 to 25 IU/l for females, and levels above this should be assessed.

• Elevated ALT or AST above the upper limit of normal (ULN) in a population without identifiable risk factors is associated with increased liver-related mortality.

• A normal ALT level may not exclude significant liver disease.

• There is a linear relationship between ALT level and body mass index (BMI) that should be assessed by physicians.

• AST and ALT ULN ranges can vary between different labs.

NON-INVASIVE IMAGING

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, Inexpensive</td>
<td>Suboptimal sensitivity/specificity for mild steatosis, Operator dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Qualitative</td>
</tr>
<tr>
<td>CT</td>
<td>High sensitivity for moderate to severe steatosis</td>
<td>Suboptimal sensitivity/specificity for mild steatosis, Radiation risks</td>
</tr>
<tr>
<td>MRI</td>
<td>Best sensitivity and sensitivity for steatosis (even mild steatosis)</td>
<td>Expensive, Limited availability as a screening tool</td>
</tr>
<tr>
<td></td>
<td>May be superior to biopsy specimen in terms of estimating total hepatic fat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Can be used to follow patients longitudinally with treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Steatosis</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>61%</td>
<td>100%</td>
</tr>
<tr>
<td>≥20%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;30%</td>
<td>79%</td>
<td>97%</td>
</tr>
</tbody>
</table>

CT, US, MRI cannot distinguish steatosis from NASH and cannot identify staging/severity (outside of advanced cirrhosis)

## NON-INVASIVE TESTING

### Fibrosis-4 (FIB-4) Index

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Interpretation</th>
<th>Sensitivity / Specificity</th>
<th>PPV / NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.30</td>
<td>Rules out advanced fibrosis</td>
<td>74% / 71%</td>
<td>43% / 90%</td>
</tr>
<tr>
<td>&gt; 2.67</td>
<td>Identifies advanced fibrosis</td>
<td>33% / 98%</td>
<td>80% / 83%</td>
</tr>
</tbody>
</table>

**Age, AST, ALT, Platelets**

**AUROC 0.80**

### NAFLD Fibrosis Score (NFS)

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Interpretation</th>
<th>Sensitivity / Specificity</th>
<th>PPV / NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; -1.455</td>
<td>Rules out fibrosis</td>
<td>77% / 71%</td>
<td>52% / 88%</td>
</tr>
<tr>
<td>&gt; 0.676</td>
<td>Predicts fibrosis</td>
<td>43% / 96%</td>
<td>52% / 88%</td>
</tr>
</tbody>
</table>

**Age, AST, ALT, Platelets, BMI, Albumin**

**Impaired fasting glucose / DM**

**AUROC 0.82**

### Enhanced Liver Fibrosis (ELF) Score

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Interpretation</th>
<th>Sensitivity / Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 9.8</td>
<td>Severe fibrosis</td>
<td>76% / 87%</td>
</tr>
<tr>
<td>≥ 11.8</td>
<td>Cirrhosis</td>
<td>38% / 97%</td>
</tr>
</tbody>
</table>

**Hyaluronic acid (HA) Procollagen III N terminal peptide (PIIINP) Tissue inhibitor of metalloproteinase-1 (TIMP1) - AUROC 0.86**

### FibroScan

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Interpretation</th>
<th>Sensitivity / Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 9.9 kPa</td>
<td>Rules in advanced fibrosis</td>
<td>95% / 77%</td>
</tr>
</tbody>
</table>

**Vibration Controlled Transient Elastography (VCTE)**
Non-invasive Fibrosis Assessment

VCTE
Point of care, accurate, operator dependent
AUROC 0.93

MR elastography
High diagnostic accuracy; limitations – cost, limited access
AUROC 0.92

Shear wave elastography
Uses acoustic radiation force impulse technology (ARFI)
Needs radiologist/sonographer
Diagnosis of NAFLD

Steatosis on imaging or suspicion based on abnormal aminotransferase levels

Assess clinical risk of steatohepatitis

- **Low Risk**
  - BMI < 30
  - No MetS features
  - Normal ALT

  Continue monitoring for new risk factors and consider liver biopsy if concern for alternate etiology

- **High Risk**
  - BMI ≥ 30
  - Diabetes
  - Dyslipidemia
  - Hypertension
  - Age > 50
  - Family history
  - Persistent ALT elevation

Assess likelihood of advanced fibrosis

- **Low Risk**
  - FIB-4 < 1.3
  - NFS < -1.455

  Continue monitoring for development of features that suggest increased risk

- **Intermediate Risk**
  - FIB-4 1.3 – 2.67
  - NFS -1.455 – 0.676

- **High Risk**
  - FIB-4 > 2.67
  - NFS > 0.676

Assess liver stiffness*

- **Low Risk**
  - VCTE, ARFI, or MRE normal

- **Intermediate Risk**
  - VCTE, ARFI, MRE intermediate, discordant with CPMs, or unavailable

- **High Risk**
  - VCTE, ARFI, MRE high

  Additional features of cirrhosis
  - Platelets < 150,000
  - Elevated INR
  - AST/ALT ratio > 0.8-1
  - Ascites
  - Splenomegaly
  - Varices
  - Portosystemic shunts

Consider liver biopsy

Clinical picture remains unclear

Management as NASH cirrhosis (consider forgoing liver biopsy)
- Monitor for liver dysfunction
- HCC screening
- Variceal screening

*Based on parameters outlined in Table 3
# NO CURRENTLY APPROVED THERAPIES FOR NASH

<table>
<thead>
<tr>
<th>Lifestyle Modification</th>
<th>Weight loss of at least 3% is associated with decreased steatosis; at least 7% for NASH resolution and at least 10% for fibrosis regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise only interventions - modest but significant effect on liver lipid even in the absence of weight loss</td>
</tr>
<tr>
<td></td>
<td>Aggressive modification of CVD risk factors should be considered in all with NAFLD</td>
</tr>
<tr>
<td>Weight Loss Surgery</td>
<td>Bariatric surgery has demonstrated improvement in NASH and metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis 15 studies: 92% improved/resolved steatosis, 82% NASH, 66% fibrosis</td>
</tr>
<tr>
<td></td>
<td>Premature specifically for NASH; can be considered in otherwise eligible obese individuals with NAFLD or NASH who meet bariatric surgery criteria</td>
</tr>
<tr>
<td>Commonly Prescribed Medications</td>
<td>Vitamin E (800 IU/day) and pioglitazone have shown mild improvements in NASH. Vitamin E not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.</td>
</tr>
<tr>
<td></td>
<td>Metformin not recommended to treat NASH. Premature to consider GLP-1 agonists specifically to treat NASH.</td>
</tr>
</tbody>
</table>

PHARMACOLOGIC TREATMENT (OFF-LABEL)

PIVENS 96 week double blind, placebo controlled, RCT phase III in adults with biopsy proven NASH and no diabetes or cirrhosis (N=247)

Vitamin E 800 IU/day
- Possible all-cause mortality risk at > 800 IU/day
- Increased hemorrhagic stroke risk
- Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; P = .008)

Pioglitazone
- Edema, weight gain (2-3 kg over 2-4 years)
- Risk of osteoporosis in women
- Equivocal bladder cancer risk
  - Increased in some studies
  - No association in most studies

Table 2: Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Vitamin E</th>
<th>Pioglitazone</th>
<th>Vitamin E vs. Placebo</th>
<th>Pioglitazone vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of subjects randomly assigned</td>
<td>83</td>
<td>84</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>19</td>
<td>43</td>
<td>34</td>
<td>0.001</td>
<td>0.04</td>
</tr>
<tr>
<td>Changes from baseline in histologic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of subjects with biopsy specimens at baseline and 96 wk</td>
<td>72</td>
<td>80</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>31</td>
<td>54</td>
<td>69</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean change in score</td>
<td>0.1</td>
<td>0.7</td>
<td>-0.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>35</td>
<td>54</td>
<td>60</td>
<td>0.02</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean change in score</td>
<td>0.2</td>
<td>0.6</td>
<td>-0.7</td>
<td>0.008</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatocellular ballooning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>29</td>
<td>50</td>
<td>44</td>
<td>0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean change in score</td>
<td>-0.2</td>
<td>-0.5</td>
<td>-0.4</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Total NAFLD activity score (mean change)</td>
<td>-0.5</td>
<td>-1.9</td>
<td>-1.9</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrosis:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>31</td>
<td>41</td>
<td>44</td>
<td>0.24</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean change in score</td>
<td>-0.1</td>
<td>-0.3</td>
<td>-0.4</td>
<td>0.19</td>
<td>0.10</td>
</tr>
<tr>
<td>Resolution of definite nonalcoholic steatohepatitis (% of subjects)</td>
<td>21</td>
<td>36</td>
<td>47</td>
<td>0.05</td>
<td>0.001</td>
</tr>
</tbody>
</table>

## NASH TREATMENTS CURRENTLY IN PHASE III INVESTIGATIONS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Trial</th>
<th>Primary Endpoint(s)</th>
<th>Time Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cenicriviroc</td>
<td>CCR2/5 antagonist</td>
<td>AURORA</td>
<td>≥ 1 stage fibrosis improvement with no NASH worsening</td>
<td>12 mos</td>
</tr>
<tr>
<td>Elafibranor</td>
<td>PPARα/σ agonist</td>
<td>RESOLVE-IT</td>
<td>Resolution of NASH with no fibrosis worsening</td>
<td>72 wks</td>
</tr>
<tr>
<td>Obeticholic acid</td>
<td>FXR agonist</td>
<td>REGENERATE</td>
<td>≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening</td>
<td>18 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>REVERSE</td>
<td>Met Primary Endpoint of fibrosis resolution but not NASH resolution in ITT analysis</td>
<td></td>
</tr>
</tbody>
</table>

- **CCR2/CCR5**
  - Blocks binding of inflammatory macrophage to hepatic stellate cell (↓ fibrosis)

- **PPARα/σ agonist**
  - PPARα - Fatty acid oxidation, ↓TG, ↑HDL, affects inflammation
  - PPARσ – Lipoprotein, glucose, energy metabolism, affects inflammation

- **FXR agonist**
  - ↓bile acids, triglycerides, Inflammation, fibrosis, ↑glucose tolerance, ↑LDL, ↓HDL
A 60 y/o old male with a history of obesity, hypertension, hyperlipidemia, type 2 diabetes mellitus presents for follow up. On prior routine laboratory testing he was found to have elevated liver tests. His liver enzymes (AST, ALT) continue to be elevated for several months. He is currently on treatment for his medical co-morbidities with lisinopril, rosuvastatin, and insulin. He has a family history notable for diabetes in his mother, and hypertension, coronary artery disease in his father. He denies a history of alcohol use, tobacco use, and illicit drug use. His BMI is 30. Otherwise, his vital signs and examination are within normal limits.

You have already performed several diagnostic studies:
Laboratory:
- Platelets: 180 k/uL
- AST 50, ALT 65, alkaline phosphatase 75 U/L, Total bilirubin 0.5 mg/dL
- Albumin 4.0 g/dL
- INR 1.0
- HbsAg negative, HCVAb negative, ANA, F-Actin smooth muscle antibody negative

You ordered an abdominal ultrasound and vibration controlled transient elastography (VCTE). Abdominal ultrasound shows increased hepatic echogenicity suggestive of hepatic steatosis, no gallstones or biliary dilation, and normal spleen size. VCTE shows 10 kPa corresponding to stage 3 hepatic fibrosis. His FIB-4 is 2.07 and NAFLD Fibrosis score is 0.277.

What is the next best management step:
A. Recommend weight loss of 3-5%
B. Start pioglitazone
C. Start vitamin E
D. Refer to Hepatology clinic for evaluation and liver biopsy
Answer: The correct answer is D.

This patient has multiple risk factors for metabolic syndrome and non-alcoholic fatty liver disease. His age, obesity, metabolic co-morbidities, and persistently elevated liver enzymes raise the concern for steatohepatitis and advanced fibrosis. NAFLD fibrosis score (NFS), Fib-4 index, VCTE, and/or MR Elastography are clinically useful tools for identifying advanced fibrosis in patients with NAFLD. FIB-4 index is an algorithm based on platelet count, age, AST, and ALT that offers dual cut-off values. Patients with score <1.45 are unlikely, whereas patients with score >3.25 are likely to have advanced fibrosis. The NFS is based on age, BMI, hyperglycemia, platelet count, albumin, AST, ALT. A score <−1.455 had 90% sensitivity and 60% specificity to exclude advanced fibrosis, whereas a score >0.676 had 67% sensitivity and 97% specificity to identify the presence of advanced fibrosis.

This patient's FIB-4 and NAFLD Fibrosis score are indeterminate for significant fibrosis. The patient's VCTE suggests advanced hepatic fibrosis (stage 3). Referral to a specialist for evaluation and liver biopsy is the best next management step. Liver biopsy should be performed in patients who are at increased risk of significant hepatic fibrosis to assess for biopsy proven non-alcoholic steatohepatitis, confirm fibrosis staging (rule out cirrhosis), and guide further management. Weight loss of at least 3%-5% of body weight appears necessary to improve steatosis, but a greater weight loss (7%-10%) is needed to improve the majority of the histopathological features of NASH, including fibrosis. Pioglitazone should not be used to treat NAFLD without biopsy-proven NASH. Vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.
PRIMARY BILIARY CHOLANGITIS

- Chronic cholestatic disease
- PBC prevalence: 0.4:1000 (AMA+ general population 1:1000)
- Female predominant > Age 40; itching; fatigue
- Immune and cellular injury to biliary epithelial cells
- Exclude primary sclerosing cholangitis
- Diagnostic criteria (2 of 3):
  - Cholestasis: ALP elevation
  - Positive AMA, or sp100 or gp210, if AMA is negative.
  - Histologic evidence of non-suppurative destructive cholangitis and destruction of interlobular bile ducts
• Treatment: UDCA dose 13-15 mg/kg/day regardless of histologic stage
• UDCA delays progression and improves survival
• Improvement in liver tests are typically observed within a few weeks, and 90% of the improvement usually occurs within 6 to 9 months. About 20% of patients will have normalization of liver biochemistries after 2 years.
• Biochemical response to UDCA should be evaluated at 12 months after treatment initiation to determine whether patients should be considered for second-line therapy.
**Binary definitions**

<table>
<thead>
<tr>
<th>Location</th>
<th>Time (months)</th>
<th>Treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochester¹</td>
<td>6</td>
<td>ALP ≥2 ULN or Mayo score ≥4.5</td>
</tr>
<tr>
<td>Barcelona²</td>
<td>12</td>
<td>Decrease in ALP ≤40% and ALP ≥1x ULN</td>
</tr>
<tr>
<td>Paris-I³</td>
<td>12</td>
<td>ALP ≥3x ULN or AST ≥2x ULN or bilirubin &gt;1 mg/dl</td>
</tr>
<tr>
<td>Rotterdam⁴</td>
<td>12</td>
<td>Bilirubin ≥1x ULN and/or albumin &lt;1x ULN</td>
</tr>
<tr>
<td>Toronto⁵</td>
<td>24</td>
<td>ALP &gt;1.67x ULN</td>
</tr>
<tr>
<td>Paris-II⁶</td>
<td>12</td>
<td>ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin &gt;1 mg/dl</td>
</tr>
<tr>
<td>Ehime⁷</td>
<td>6</td>
<td>Decrease in GGT ≤70% and GGT ≥1 ULN</td>
</tr>
</tbody>
</table>

**Continuous scoring**

<table>
<thead>
<tr>
<th>Location</th>
<th>Time (months)</th>
<th>Scoring parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK-PBC⁸</td>
<td>12</td>
<td>12 months: bilirubin, ALP and AST (or ALT); Baseline: albumin and platelets</td>
</tr>
<tr>
<td>GLOBE⁹</td>
<td>12</td>
<td>12 months: bilirubin, ALP, albumin, and platelet count; Baseline: age</td>
</tr>
</tbody>
</table>

*2203/3161 patients were included for this analysis

*2109/3161 patients were included for this analysis
• Patients who are inadequate responders to UDCA (>1 year) should be considered for treatment with OCA or as monotherapy in those intolerant to UDCA

• OCA is an Farnesoid X receptor (FXR) agonist → protects against bile acid toxicity; impairs bile acid synthesis and upregulates bile acid transporters; anti-inflammatory and anti-fibrotic effects

Phase 3 study (N=216); 93% on UDCA. Primary Endpoint ALP<1.67xULN with reduction at least 15% from baseline and normal total bilirubin.
OCA side effects: Pruritus common side effect (up to 50% in study), ↓HDL, ↓TG, ↑LDL

Use of OCA is discouraged in patients with decompensated liver disease (Child-Pugh-Turcotte B or C)

BOXED WARNING

- In post-marketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in patients with primary biliary cholangitis (PBC) with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when obeticholic acid was dosed more frequently than recommended.
- The recommended starting dosage of obeticholic acid is 5 mg once weekly for patients with Child-Pugh Class B or C hepatic impairment or a prior decompensation event.

<table>
<thead>
<tr>
<th>Obeticholic acid dosing</th>
<th>Non-cirrhotic or Child Pugh A</th>
<th>Child Pugh B or C or prior decompensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting for first 3 months</td>
<td>5 mg once daily</td>
<td>5 mg once weekly</td>
</tr>
<tr>
<td>Titration after first 3 months (inadequate alkaline phosphatase and/or total bilirubin response)</td>
<td>10 mg once daily</td>
<td>5 mg twice weekly (at least 3 days apart)</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>10 mg once daily</td>
<td>10 mg twice weekly (at least 3 days apart)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points Scored for Observed Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy grade</td>
<td>1 point</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>International Normalized Ratio (INR)</td>
<td>&lt; 1.7</td>
</tr>
</tbody>
</table>

Child-Pugh Class is obtained by adding the points from all 5 parameters to derive a total score, which can range from 5 to 15 points. Total Score: 5-6 points = A, 7-9 points = B, 10-15 points = C
PRIMARY BILIARY CHOLANGITIS

- Manage pruritus (anion exchange resins such as cholestyramine; if refractory – rifampicin, naltrexone, and/or sertraline)
- TSH annually
- Bone mineral densitometry every 2 years
- Vitamins A, D, E and prothrombin time annually if bilirubin >2.0
- Upper endoscopy every 1-3 years if cirrhotic, Mayo risk score >4.1, or transient elastography shows a score ≥17 kPa
- Ultrasound with or without alpha fetoprotein in patients with known or suspected cirrhosis and men every 6 months
- Patients with manifestations of end-stage PBC should be referred for liver transplantation when their MELD-Na score exceeds 14.

HEPATITIS C

- RNA virus discovered 1988
- 6 genotypes (Genotype 1 accounts for 79% infections in US)
- First therapy approved 1991
- SVR 40-50% prior to 2011
- 3.5 million chronically infected (US) [2003-2013]
  - 75% born 1945-1965
  - 50% diagnosed and aware
  - 16% prescribed therapy

• Bimodal distribution
• 30,500 new infections (2014)
• Previously highest group infected were those born 1945-1965, now more in younger age demographic due to IV drug use

HCV Infection

15-25% HCV spontaneous clearance (within 6 months of exposure)

75-85% Chronic infection

10-20% Cirrhosis (over 20 years)

Extrahepatic manifestations:

- Mixed cryoglobulinemia
- Sjogren syndrome
- Lymphoproliferative disorders
- Porphyria cutanea tarda
- Neuropathy
- Membranoproliferative glomerulonephritis
- Cryoglobulinemic vasculitis

RATIONALE FOR TREATMENT - SUSTAINED VIROLOGIC RESPONSE (SVR)

Welcome to HCVGuidelines.org

The AASLD and IDSA in partnership with the panel have created an updated web experience to facilitate easier and faster access to this important resource. Please select a patient profile from the menu above, click on a guidance section below, or use the search box to begin.

- Contents and Introduction - Select a Page
- Testing, Evaluation, and Monitoring of Hepatitis C - Browse Topics
- Initial Treatment of HCV Infection - Choose Patient Genotype
- Retreatment of Persons in Whom Prior Therapy Has Failed - Choose Patient Genotype
- Management of Unique & Key Populations - Review Recommendations
PRE-TREATMENT

• One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older
• One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection
• Periodic repeat HCV testing should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure
• Annual HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men

• Risk Behaviors: IVDU, intranasal illicit drug use, MSM
• Risk Exposures: Hemodialysis, healthcare exposure, children born to HCV+ women, transfusion (before 1992), incarceration, HIV, chronic liver disease, organ donors/recipients

AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Updated 11/6/19
PRE-TREATMENT

- Alcohol abstinence recommended

- Evaluate for HBV, HIV
  - Treat HBV if meets guidelines
  - HBV reactivation risk - DAA black box warning
  - HbsAg+ → Treat if meets criteria
    - If not meeting criteria, treat prophylactically or monitor HBV DNA monthly during and after therapy; treat if HBV DNA >10-fold or >1000 IU/mL if previously undetectable or unquantifiable
  - HbsAg-/HbcAb+ → Check HBV DNA if ALT increases and initiate treatment if HBV DNA +

- Evaluate for advanced fibrosis

- Vaccinate against hepatitis A and B
- Vaccinate against pneumococcal infection (cirrhosis)
- Educate about preventing transmission to others
- Evaluate for treatment drug-drug interactions
- Be cautious of drug-drug interactions
- Avoid amiodarone, dronedarone (severe contraindication with sofosbuvir based regimens)
- SOF/VEL – Avoid PPI; H2RA preferred. Omeprazole 20 mg with food 4 hours prior if cannot use/tolerate H2RA
- SOF/VEL – Pravastatin 20 mg preferred; Rosuvastatin max 10 mg
- GLE/PIB – Avoid atorvastatin, simvastatin, lovastatin
  Pravastatin reduce 50%
  Rosuvastatin max 10 mg
- Most anticonvulsants, barbiturates, first generation antipsychotics should be avoided. Avoid Bosentan, St John’s wort, rifamycin antimicrobials

www.hep-druginteractions.org

# TREATMENT NAIVE WITHOUT CIRRHOSIS

## ELIGIBLE

Patients with chronic hepatitis C who do not have cirrhosis and have not previously received Hepatitis C treatment

## NOT ELIGIBLE

Patients who have any of the following characteristics:
- Prior hepatitis C treatment
- Cirrhosis
- Prior liver transplant
- HIV or HBsAg positive
- Currently pregnant

## PRETREATMENT ASSESSMENT

### Cirrhosis Assessment
- Biopsy not required
- Cutoffs suggesting cirrhosis:
  - FIB-4 >3.25
  - APRI >2.0
  - Platelets <150,000/mm³
  - VCTE >12.5 kPa

### Pretreatment Lab Testing

- **Within 6 months**
  - CBC
  - Hepatic function panel
  - eGFR
- **Prior to starting antiviral therapy**
  - Quantitative HCV RNA (HCV viral load)
  - HIV antigen/antibody test
  - HBsAg

### Medication Reconciliation
- Current Rx and OTC

### DDI Assessment

### Education
- Tx administration, adherence, avoidance of alcohol, and reinfection

### Before initiating Tx
- Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

## RECOMMENDED REGIMENTS

**Sofosbuvir/Velpatasvir (SOF/VEL)** for a duration of 12 weeks

**Glecaprevir/Pibrentasvir (GLE/PIB)** to be taken with food for a duration of 8 weeks

AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Updated 11/6/19
**TREATMENT NAIVE WITH CIRRHOSIS**

### ELIGIBLE

- Treatment-Naïve adults with chronic hepatitis C (any genotype) who have compensated cirrhosis (Child-Pugh A). Liver biopsy is not required.
- Patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or any of the following findings from a previously performed test:
  - Transient elastography indicating cirrhosis
  - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis
  - Clinical evidence of cirrhosis (e.g., liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm³, etc)
  - Prior liver biopsy showing cirrhosis

### NOT ELIGIBLE

Patients who have any of the following characteristics:

- Current or prior episode of decompensated cirrhosis, defined as Child-Turcotte-Pugh (CTP) score ≥7 (ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7)
- Prior hepatitis C treatment
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

### RECOMMENDED REGIMENS

- **GT 1, 2, 3*, 4, 5, or 6**
  - **SOF/VEL**
  - for a duration of 12 weeks
  
- *GT3: 12 weeks without NS5A Y93H RAS (If present, refer to HCV guidance)*

- **GT 1-6**
  - **GLE/PIB**
  - taken with food for a duration of 8 weeks

---

AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Updated 11/6/19
DURING AND AFTER TREATMENT

• Educate regarding potential for hypoglycemia
• Monitor for coagulation changes in those on warfarin
• Discontinue therapy if 10-fold ALT increase or less than 10-fold increase if symptomatic
• For those with SVR, check HCV PCR (not Ab) if unexplained hepatic dysfunction or annually if ongoing risk factors
• **Non-cirrhotic**
  • Assess hepatic function and HCV RNA 12 weeks after therapy
  • No specific follow up needed for non-cirrhotics who achieve SVR who do not have advanced fibrosis
• **Cirrhotics**
  • Calculate Child Pugh score, obtain imaging (±AFP) for HCC screening, EGD for variceal screening, MELD-Na labs every 6 months

AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Updated 11/6/19
UNIQUE SITUATIONS

- HCV treatment not recommended for those with short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or other therapy
- Do not treat decompensated liver disease or Child Pugh B/C with NS3 protease inhibitors (e.g. glecaprevir, grazoprevir, voxilaprevir) or interferon based regimens
- Ribavirin (RBV) containing regimens – Check pregnancy testing prior. No pregnancy until at least 6 months after completing treatment; contraceptive methods encouraged
- Pregnancy
  - Treat before if possible to prevent perinatal transmission. MFM consultation.
  - Evaluate HCV PCR after delivery to assess for spontaneous clearance.
  - Breastfeeding not contraindicated (unless cracked, damaged, bleeding nipples or HIV co-infection)
  - Children should be tested ≥18 months (HCVAb). If positive, test HCV RNA after age 3 to confirm infection. RNA testing can be done as early as 2 months. Siblings of HCV+ children should be tested.
UNIQUE SITUATIONS

- **Renal impairment**
  No dose adjustment (Ribavirin reduction may be required for CKD3-5)

- **HCV/HIV Co-infection**
  Cautious of multiple drug-drug interactions

- **Cirrhosis / Solid organ transplant**
  Refer to Hepatology

- **Persons Who Inject Drugs (PWID)**
  Substance use, needle/syringe exchange programs; naloxone; treatment and linkage to care
  Active/recent drug use: Not a contraindication to treatment

- **Incarceration**
  Treatment recommended and linkage to care

- **Children**
  Treatment naive with or without cirrhosis
  \[ \geq \text{age 3} \] (weight based sofosbuvir/ledipasvir GT1,4,5,6 x 12 weeks)
  \[ \geq 12 \text{ or } \geq 45 \text{ kg} \] (GLE/PIB x 8 weeks)

- **Treatment Failure with prior DAA NS5A**
  Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX) x 12 weeks; add RBV if GT 3 cirrhotic

  GLE/PIB Exposure ⇒ GLE/PIB + SOF + RBV x 16 weeks or SOF/VEL/VOX x 12 weeks (RBV if cirrhotic)
  SOF/VEL/VOX Failure ⇒ GLE/PIB + SOF + RBV x 16 weeks or SOF/VEL/VOX+RBV x 24 week
Low risk of late re-infection/relapse in low, high risk, and co-infected groups

Meta-analysis 61 studies (n=9049)
LIVER TRANSPLANT

>100,000 transplants since 1985

80% 5 year survival

70% 10 year survival
IMMUNOSUPPRESSION

Steroids

• Toxicity: infection, bone loss, hypertension, diabetes, dyslipidemia, emotional lability

Calcineurin inhibitors (*Tacrolimus, Cyclosporine*)

• Inhibits calcineurin and IL-2
• Toxicity: nephrotoxicity, neurotoxicity, hypertension, diabetes, dyslipidemia, hirsutism/gingival hyperplasia (CYA)

Anti-proliferatives (*Mycophenolate, Azathioprine*)

• Inhibits B and T-cell proliferation
• Bone marrow suppression, cytopenias, GI disturbances

mTOR inhibitors (*Everolimus, Sirolimus*)

• Reduces IL-2 mediated B and T-cell proliferation
• Toxicity: hyperlipidemia, proteinuria, edema, pulmonary fibrosis, hepatic artery thrombosis, ↓ wound healing

Lucey at al. AASLD Practice Guideline. Liver Transplantation 19:3-26, 2013
### TABLE 4. Major Drug-Drug Interactions Involving Immunosuppressive Agents

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>CNIs</th>
<th>mTOR Inhibitors</th>
<th>Mycophenolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones (primarily ofloxacin &gt; ciprofloxacin)</td>
<td>Increased levels</td>
<td>Markedly increased levels</td>
<td>Markedly increased levels and platelet decrease</td>
</tr>
<tr>
<td>Macrolides (erythromycin &gt; clarithromycin &gt; azithromycin)</td>
<td>Markedly increased levels</td>
<td>Markedly decreased levels</td>
<td>Increased myelosuppression and platelet decrease</td>
</tr>
<tr>
<td>Rifamycins (rifampin &gt; rifabutin)</td>
<td>Markedly decreased levels</td>
<td>Markedly decreased levels</td>
<td>Increased myelosuppression</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Increased myelosuppression</td>
<td>Increased levels (voriconazole contraindicated)</td>
<td>Increased myelosuppression</td>
</tr>
<tr>
<td>Triazoles (ketoconazole/ voriconazole/ posaconazole &gt; itraconazole/ fluconazole)</td>
<td>Increased levels</td>
<td>Increased levels (voriconazole contraindicated)</td>
<td>Increased myelosuppression</td>
</tr>
<tr>
<td>Ganciclovir/valganciclovir</td>
<td>Increased myelosuppression</td>
<td>Increased levels (voriconazole contraindicated)</td>
<td>Increased myelosuppression</td>
</tr>
</tbody>
</table>

### TABLE 2. Prevalence of Cardiovascular Risk Factors and CKD in LT Recipients Beyond the First Posttransplant Year

<table>
<thead>
<tr>
<th>Cardiovascular risk factor</th>
<th>Prevalence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome*</td>
<td>50%-60%</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>40%-85%</td>
</tr>
<tr>
<td>DM</td>
<td>10%-64%</td>
</tr>
<tr>
<td>Obesity</td>
<td>24%-64%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>40%-66%</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>10%-40%</td>
</tr>
<tr>
<td>CKD (stage 3-4)†</td>
<td>30%-80%</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>5%-8%</td>
</tr>
</tbody>
</table>
LIVER TRANSPLANT OUTCOMES

- High infection risk - CMV prophylaxis (3 months), fungal ppx (3-12 months), PJP ppx (6-12 months)
- Any CV event (10%); NASH (25%), metabolic syndrome (30%) – ACS (42%), CHF (22%), Stroke (11%), Arrhythmia, Peripheral vascular disease
- New onset diabetes in up to 26% at 1 year
- New obesity 20-30% within 2-3 years post transplant (improved health, appetite)
- 50-70% of NASH patients will gain excessive weight in 1 year post transplant
- Renal failure → 10% death after 5 years
  - Stage 4 CKD 8% at 1 year, 14% 3 years, 18% 5 years, 25% 10 years
  - CNI vasoconstricts renal afferent arterioles → decreased renal perfusion, tubular ischemia + glomerular injury from metabolic risk factors
  - Renal sparing strategy: lower CNI goals or mTOR inhibitors (±MMF)
- Low bone mineral density in up to 70% of those with liver disease

LONG-TERM LIVER TRANSPLANT OUTCOMES

• Malignancy 2-4x higher than general population (2-16% patients)
• De novo malignancy risk: 3.5% at 1 year, 11.9% at 5 years, 21.7% at 10 years
• 10 year probability (GI, lung, female GU, oropharyngeal/laryngeal cancer): 3.6, 2, 1.8, 1.1%
• Skin cancers up to 100x more common than general population
• Post-transplant lymphoproliferative disorder: 2.8% (adult), 15% (pediatric recipients), EBV associated 90%
• Colorectal cancer screening: Every 5-10 years (annual if history of PSC/ulcerative colitis)
• mTOR inhibitors have potential anti-cancer effect in those transplanted for HCC

<table>
<thead>
<tr>
<th>TABLE 10. Relative Risks of De Novo Malignancies in LT Recipients Versus a Sex- and Age-Matched Population</th>
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</thead>
<tbody>
<tr>
<td>Malignancy</td>
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<tr>
<td>Skin cancers</td>
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<tr>
<td>Squamous and basal cell carcinoma</td>
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<tr>
<td>Melanoma</td>
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<tr>
<td>Lymphoma</td>
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<tr>
<td>Oropharyngeal cancer, including esophageal cancer</td>
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<td>(as high as 25%) if the prior diagnosis was alcoholic cirrhosis</td>
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<tr>
<td>Lung cancer</td>
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<tr>
<td>Colorectal cancer</td>
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<td>Kidney cancer</td>
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</tbody>
</table>

LONG-TERM LIVER TRANSPLANT CARE

**Hypertension:** BP<140/90 or <130/80 with DM, CKD, CAD
CCB (amlodipine, nifedipine) and/or ACEI/ARB first line. Avoid diltiazem, verapamil

**Diabetes:** Monitor closely until off steroids, then every 3-6 months for 1 year, then annually

**Dyslipidemia:** ASVD Risk. LDL<100 mg/dL. Statins, fish oil/fibrates (elevated TG), refractory hyperlipidemia → immunosuppression reduction or change

**CAD:** ASA prophylaxis

**CKD:** Optimize DM, HTN. Avoid nephrotoxic medications (NSAID’s). Annual urine prot/creat

**Bone health:** DEXA every 2-3 years, 1500 mg calcium, 800 IU Vitamin D

**Depression/PTSD:** SSRI first line (minimal inhibition of CYP450)

**Pregnancy:** High risk; delay for at least 1 year post OLT
↑pre-eclampsia, prematurity, low birth weight, ↑congenital malformations (4-5% vs 3%)
CNI should be continued through pregnancy. Avoid/stop MMF. Breastfeeding controversial.

LONG-TERM LIVER TRANSPLANT CARE

Recommendations

• Treatment and prevention of metabolic complications
• Age appropriate cancer screening
• Annual dermatology visit for skin cancer screening; SPF, protective clothing
• No live vaccines; influenza, pneumovax-23, prevnar-13, Tdap, HAV/HBV, H.flu (s/p splenectomy) recommended. Delay vaccinations until prednisone <10 mg/day
• Smoking cessation
• Alcohol abstinence
• Minimize tick, mosquito exposure; avoid river/lake water consumption
• Avoid unpasteurized food, raw/undercooked: eggs, seafood, meat, chicken, pork
• Avoid high risk pets (rodents, reptiles, chicks, ducklings, birds)

THANK YOU

QUESTIONS?