Hepatitis B & C
Diagnosis & Treatment
Case Studies

Hepatitis: Preventing the Silent Epidemic in Kentucky
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Disclosures

Jens Rosenau, MD, has disclosed that he has received consulting fees from Gilead.

The slides will discuss uses and dosages for therapeutic products that have not been approved by the United States Food and Drug Administration.
Hepatitis C
Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy, is recommended for all persons with current (active) HCV infection.

AASLD/IDSA Guidelines
www.hcv-guidelines.org
HCV Case 1: GT 1b, Tx naïve, non-cirrhotic

- 32 yo Caucasian female
- Injection drug use from 2 years ago until 2 months ago, currently in drug rehab program on suboxone treatment, intranasal drug use from age 18 to 25, multiple tattoos from age 15 to 25
- Screening of asymptomatic patient with HCV risk factors reveals positive Anti-HCV antibody (8 weeks ago)

- ALT 330 IU/mL, AST 290 IU/mL, Bilirubin 0.8 mg/dL, INR 1.0, Platelets 280,000/mm3 (all 4 weeks ago)
- HCV RNA 25,000 IU/mL, Genotype 1b (all 4 weeks ago)

- Patient asks for HCV treatment options
AASLD/IDSA: When and in Whom to Initiate HCV Therapy

- **ALL** pts are candidates for HCV therapy, regardless of disease stage
- In regions where limited resources preclude treatment of all pts, the following groups should be prioritized for therapy:
  - **Highest Priority** (based on highest risk for disease complications)
    - Advanced fibrosis (F3) or compensated cirrhosis (F4)
    - Organ transplant
    - Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations
    - Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
  - **High Priority** (based on high risk for disease complications)
    - HIV-1 coinfection
    - Fibrosis (Metavir F2)
    - HBV coinfection
    - Debilitating fatigue
    - Other coexistent liver disease (eg, NASH)
    - Type 2 DM (insulin resistant)
    - Porphyria cutanea tarda

HCV Treatment Improves Health

**Advanced fibrosis**
- Multicenter study[^1]
  - 5 hospitals (Europe, Canada)
  - 530 pts with HCV
  - IFN regimens 1990-2003
  - Advanced fibrosis or cirrhosis
  - Median follow-up: 8.4 yrs

**Early-stage disease**
- Extra-hepatic manifestations[^2]
- Health-related quality of life[^3]

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Key Data for HCV treatment decisions

- HCV Genotype

- HCV treatment history
  - Interferon and ribavirin regimen?
  - Protease inhibitor? NS5a inhibitor? Sofosbuvir?

- Fibrosis stage?
  All patients should be staged to determine if they are cirrhotic
  - Cirrhotics have somewhat reduced likelihood of SVR with some current therapies
  - Cirrhotics need screening for HCC and varices

- If cirrhosis, is it decompensated?
  Child Pugh B or C?

Transplant evaluation?

http://www.hcvguidelines.org
How Would You Assess Fibrosis?

- **Liver Biopsy**
  - Few experts are performing biopsy on a regular basis
  - Reserved for when other methods provide insufficient information

- **Serum Panels**
  - APRI AST, platelets
  - FIB-4 age, AST, ALT, platelets
  - Fibrosure 3 proteins, Bilirubin, ALT, GGT
  - Direct markers of extracellular matrix turnover

- **Ultrasound-based shear wave elastography**
  - Vibration Controlled Transient Elastography (VCTE): Fibroscan
  - Acoustic Radiation Force Impulse (ARFI)

- **Magnetic Resonance Elastography (MRE)**
HCV Case 1: GT 1b, Tx naïve, non-cirrhotic

- 34 yo Caucasian female
- Injection drug use about 2 years ago for about 4 months, intranasal drug use from age 18 to 25, multiple tattoos from age 15 to 25
- Screening of asymptomatic patient due to risk factors reveals positive Anti-HCV antibody
- ALT 60 IU/mL, AST 45 IU/mL, Bilirubin 0.8 mg/dL, INR 1.0, Platelets 280,000/mm3
- HCV RNA 2,300,000 IU/mL, Genotype 1b
- FIB 4 score 1.05 (advanced fibrosis unlikely with score <1.45)
- Fibrosure score: 0.08 c/w low fibrosis
- Planning pregnancy, concerned about HCV transmission
### Genotype 1 HCV Agents

<table>
<thead>
<tr>
<th>Protease Inhibitors</th>
<th>Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir</td>
<td>Sofosbuvir</td>
<td>Ledipasvir</td>
<td>Ribavirin</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir</td>
<td>Dasabuvir</td>
<td>Ombitasvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daclatasvir</td>
<td></td>
</tr>
</tbody>
</table>
# Genotype 1 HCV: AASLD/IDSA-Recommended Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Genotype 1</th>
<th>Regimen Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simeprevir + peginterferon + ribavirin</td>
<td>Not recommended</td>
<td>QD-QWK; multiple tablets + injection</td>
</tr>
<tr>
<td>Sofosbuvir + peginterferon + ribavirin</td>
<td>Not recommended</td>
<td>QD-QWK; multiple tablets + injection</td>
</tr>
<tr>
<td>Sofosbuvir + ribavirin</td>
<td>Not recommended</td>
<td>QD; multiple tablets</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>Recommended</td>
<td>QD; single-tablet regimen</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/ritonavir, dasabuvir, ± ribavirin</td>
<td>Recommended</td>
<td>QD-BID; multiple tablets</td>
</tr>
<tr>
<td>Simeprevir + sofosbuvir ± ribavirin</td>
<td>Recommended</td>
<td>QD; multiple tablets</td>
</tr>
</tbody>
</table>

http://www.hcvguidelines.org
# Genotype 1 HCV Treatment Naive

- AASLD-IDSA guidelines
  - 3 regimens recommended

<table>
<thead>
<tr>
<th>Genotype 1a, no cirrhosis</th>
<th>Ledipasvir/Sofosbuvir*</th>
<th>Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir</th>
<th>Simeprevir + Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 wks</td>
<td>12 wks + RBV</td>
<td>12 wks ± RBV</td>
</tr>
<tr>
<td>Genotype 1a, cirrhosis</td>
<td>12 wks</td>
<td>24 wks + RBV</td>
<td>24 wks ± RBV</td>
</tr>
<tr>
<td>Genotype 1b, no cirrhosis</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
</tr>
<tr>
<td>Genotype 1b, cirrhosis</td>
<td>12 wks</td>
<td>12 wks + RBV</td>
<td>24 wks</td>
</tr>
</tbody>
</table>

*Ledipasvir/sofosbuvir for 8 wks can be considered in naive, noncirrhotic pts with baseline HCV RNA < 6 million IU/mL.

http://www.hcvguidelines.org
## Genotype 1 HCV Treatment Naive Noncirrhotic

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Wks</th>
<th>Study</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ledipasvir/sofosbuvir (HCV RNA &lt; 6 M IU/mL)</td>
<td>8</td>
<td>ION-3(^{[1,2]})</td>
<td>119/123 (97%)</td>
</tr>
<tr>
<td>Ledipasvir/sofosbuvir</td>
<td>12</td>
<td>ION-3(^{[1]})</td>
<td>206/216 (95%)</td>
</tr>
</tbody>
</table>
| Simeprevir + sofosbuvir*                                              | 8-12| OPTIMIST-1\(^{[3]}\) | 8 wks: 128/155 (83%)
|                                                                       |     |                    | 12 wks: 150/155 (97%)    |
| Ombitasvir/paritaprevir/ritonavir, dasabuvir (GT1b)                    | 12  | PEARL III\(^{[4]}\) | 207/209 (99%)            |
| Ombitasvir/paritaprevir/ritonavir, dasabuvir, ribavirin (GT1a)         | 12  | PEARL IV\(^{[4]}\)  | 97/100 (97%)             |
| Sofosbuvir + daclatasvir                                              | 12  | AI444040\(^{[5]}\) | 41/41 (100%)             |

*GT1a + Q80K-8 wks: 36/49 (73%); GT1a + Q80K-12 wks: 44/46 (96%).*

HCV Case 2: GT 1a, Tx experienced, cirrhotic

- 54 yo Caucasian male
- H/o injection drug use in 1980s
- H/o chronic hepatitis C with HCV Tx with PegIFN plus Ribavirin in 2005, treatment was discontinued after 4 months due to insufficient response

- ALT 45 IU/mL, AST 55 IU/mL, ALP 130 IU/mL, Bilirubin 0.8 mg/dL, INR 1.0, Platelets 79,000/mm3, Creatinine 1.5 g/dL, eGFR 45, h/o CAD
- HCV RNA positive, Genotype 1a
- Fibrosure score: 0.85 c/w advanced fibrosis/cirrhosis

- U/S: Nodular appearance of the liver, mild splenomegaly, no ascites
- EGD: Esophageal varices grade 1
# Genotype 1 HCV PegIFN/RBV Treatment Experienced

- AASLD-IDSA guidelines
  - 3 regimens recommended

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Ledipasvir/ Sofosbuvir</th>
<th>Ombitasvir/ Paritaprevir/ Ritonavir + Dasabuvir</th>
<th>Simeprevir + Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, no cirrhosis</td>
<td>12 wks</td>
<td>12 wks + RBV</td>
<td>12 wks</td>
</tr>
<tr>
<td>Genotype 1a, cirrhosis</td>
<td>24 wks</td>
<td>24 wks + RBV</td>
<td>24 wks ± RBV if Q80K neg</td>
</tr>
<tr>
<td></td>
<td>12 wks + RBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1b, no cirrhosis</td>
<td>12 wks</td>
<td>12 wks</td>
<td>12 wks</td>
</tr>
<tr>
<td>Genotype 1b, cirrhosis</td>
<td>24 wks</td>
<td>12 wks + RBV</td>
<td>24 wks ± RBV</td>
</tr>
<tr>
<td></td>
<td>12 wks + RBV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

http://www.hcvguidelines.org
Newer Combination DAA-Experienced Pts Will Appear in Your Practice

- Sofosbuvir + simeprevir
- Ledipasvir/sofosbuvir
- Ombitasvir/paritaprevir/ritonavir + dasabuvir

- Failure of newer DAA regimens generally presents as relapse with RAVs to at least 1 class
### DAAs: Barrier to Genetic Resistance

<table>
<thead>
<tr>
<th></th>
<th>Protease Inhibitors</th>
<th>Nucleos(t)ide Polymerase Inhibitors</th>
<th>Nonnucleoside Polymerase Inhibitors</th>
<th>NS5A Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrier to resistance</td>
<td>Low ((1a &lt; 1b))</td>
<td>High ((1a = 1b))</td>
<td>Very low ((1a &lt; 1b))</td>
<td>Low ((1a &lt; 1b))</td>
</tr>
<tr>
<td>Comments</td>
<td>2nd-generation PIs have higher barrier, pangenotypic</td>
<td>Single target Active site</td>
<td>Allosteric Many targets</td>
<td>Multiple antiviral MOA</td>
</tr>
</tbody>
</table>

- RAVs to 1 drug are generally cross-resistant to other drugs within a class, although this is not always the case.
- Viral fitness of RAVs effects their persistence after d/c of tx
  - RAV viral fitness varies between drug classes
- Identification and characterization of full resistance profiles for newer DAAs is rapidly evolving
- Drug resistance needs to be considered for each pt needing retreatment after DAA failure

Persistence of RAVs Varies by Drug Class

- NS3/4 RAVs generally short-lived
  - Majority of pts had only WT NS3 at mean 4.23 yrs after end of treatment with telaprevir or boceprevir[1]

- NS5A RAVs demonstrate viral fitness and persist; may present barrier to future retreatment
  - 86% of pts who experienced failure of LDV-containing regimens without SOF harbored NS5A RAVs 96 wks after treatment discontinuation[2]
    - Number of RAVs per pt decreased over time

HCV Case 3: GT1a, Tx experienced SOF/LDV, advanced fibrosis

- 45 yo Caucasian male
- H/o intranasal drug use (cocaine) in 1990s, multiple nonprofessional tattoos, h/o heavy alcohol use
- Liver biopsy in 8/2014 showed Metavir stage 3 fibrosis
- Relapse after 8 weeks of HCV treatment with Harvoni (sofosbuvir plus ledipasvir)

- ALT 45 IU/mL, AST 42 IU/mL, Bilirubin 0.8 mg/dL, INR 1.0, Platelets 152,000/mm3
- HCV RNA 3,350,000 IU/mL, Genotype 1a
- U/S 3/2015: Coarse echotexture of the liver, spleen 14 cm, no ascites
24-Wk LDV/SOF After Failure of 8-12 Wks of LDV/SOF-Based Therapy in GT1 Pts

- Results from single arm of prospective phase II trial evaluating LDV/SOF for 24 wks in 41 pts with GT1 HCV infection previously treated with LDV/SOF-based therapy

- NS5B variants emerged during retreatment in 33% of pts (4/12) with VF
  - S282T: n = 2; L159F: n = 1; S282T + L159F: n = 1

HCV Case 4: GT3, Tx experienced, compensated cirrhosis

- 54 yo Caucasian male
- H/o injection drug use in 1980s
- H/o HCV treatment x 3:
  1. Standard IFN plus RBV in 2000, relapse
  2. PegIFN plus RBV for 48 weeks in 2005, relapse
  3. PegIFN plus higher dose RBV for 72 weeks in 2012, relapse

- ALT 45 IU/mL, AST 55 IU/mL, ALP 130 IU/mL, Bilirubin 0.8 mg/dL, INR 1.0, Platelets 79,000/mm3
- HCV RNA 8,350,000 IU/mL, Genotype 3

- Liver biopsy in 2005 showed Metavir stage 4 fibrosis (cirrhosis)
- U/S: Nodular appearance of the liver, mild splenomegaly, no ascites
- EGD: No signs of portal hypertension.
Genotypes 2 and 3

- AASLD-IDSA guidelines

<table>
<thead>
<tr>
<th>Genotype 2</th>
<th>Sofosbuvir + Ribavirin</th>
<th>Peginterferon-α, Ribavirin + Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>12 wks (16 wks for cirrhosis)</td>
<td>None</td>
</tr>
<tr>
<td>PegIFN/RBV nonresponders</td>
<td>12-16 wks</td>
<td>12 wks (alternative)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 3</th>
<th>Peginterferon-α, Ribavirin + Sofosbuvir</th>
<th>Sofosbuvir + Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naive</td>
<td>12 wks</td>
<td>24 wks (alternative)</td>
</tr>
<tr>
<td>PegIFN/RBV nonresponders</td>
<td>12 wks</td>
<td>24 wks (alternative)</td>
</tr>
</tbody>
</table>

http://www.hcvguidelines.org
**BOSON: SVR12 With SOF-Based Regimens in GT3 by Tx History and Cirrhosis Status**

<table>
<thead>
<tr>
<th>SVR12 (%)</th>
<th>SOF + RBV 16 wks</th>
<th>SOF + RBV 24 wks</th>
<th>SOF + PegIFN/RBV 12 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Naive</td>
<td>83/70</td>
<td>65/72</td>
<td>68/71</td>
</tr>
<tr>
<td></td>
<td>57/21</td>
<td>18/22</td>
<td>21/23</td>
</tr>
<tr>
<td></td>
<td>41/54</td>
<td>44/54</td>
<td>49/52</td>
</tr>
<tr>
<td></td>
<td>17/36</td>
<td>26/34</td>
<td>30/35</td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Naive</td>
<td>90/70</td>
<td>82/72</td>
<td>96/71</td>
</tr>
<tr>
<td></td>
<td>82/22</td>
<td>91/23</td>
<td>94/23</td>
</tr>
<tr>
<td></td>
<td>82/54</td>
<td>76/54</td>
<td>82/52</td>
</tr>
<tr>
<td></td>
<td>77/36</td>
<td>77/34</td>
<td>86/35</td>
</tr>
</tbody>
</table>

**Clinical Options**

**Daclatasvir + Sofosbuvir in Tx-Naive and Tx-Exp’d Pts With Genotype 3 HCV**

**ALLY-3**\(^1\)

**Pts:**
- Treatment naive and experienced
  - Prior sofosbuvir and alisporivir included
  - Prior NS5A inhibitors excluded
  - Cirrhosis: 21%

**Design**
- 2 open-label cohorts
- Phase III

**Regimen**
- Daclatasvir + sofosbuvir once daily for 12 wks

**SVR12 (%)**

<table>
<thead>
<tr>
<th></th>
<th>Naive</th>
<th>Experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cirrhosis</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>58</td>
<td>69</td>
</tr>
</tbody>
</table>

**EASL recommendations for DCV + SOF in GT3**\(^2\)
- No cirrhosis: DCV + SOF for 12 wks
- Compensated cirrhosis: DCV + SOF + RBV for 24 wks

Special Populations
Decompensated Liver Cirrhosis: Natural History of Chronic Liver Disease

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Development of complications:
- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice

Decompensation Shortens Survival

All pts with cirrhosis
Median survival ~ 9 yrs

Decompensated cirrhosis
Median survival ~ 1.6 yrs

## Assessing Cirrhosis Severity: Child-Pugh Score

<table>
<thead>
<tr>
<th>Variable Points</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy grade</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Prothrombin time (sec prolonged)</td>
<td>&lt; 4</td>
<td>4-6</td>
<td>&gt; 6</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2-3</td>
<td>&gt; 3</td>
</tr>
</tbody>
</table>

- **Child-Pugh A**: 5-6 points
- **Child-Pugh B**: 7-9 points
- **Child-Pugh C**: ≥ 10 points

Subjective component relies on clinical judgment

HCV Case 5: Genotype 1a, treatment naive, decompensated cirrhosis

- 60 yo Caucasian female
- H/o injection drug use in 1980s, h/o heavy alcohol use for about 10 years, quit in 11/2014
- H/o decompensation with large ascites in 11/2014, currently controlled on treatment with 25 mg spironolactone daily
- Hepatic encephalopathy: Sleep disturbances, forgetfulness, denies hospitalizations

- ALT 32 IU/mL, AST 45 IU/mL, Bilirubin 2.3 mg/dL, INR 1.2, Platelets 54,000/mm3, Albumin 3.1 g/dL: MELD score 12; CPT score 9, Child class B
- HCV RNA positive, Genotype 1a

- U/S: Nodular appearance of the liver, splenomegaly, trace ascites
- EGD: Esophageal varices grade 2, no h/o variceal bleeding, on primary bleeding prophylaxis with nadolol 20 mg daily
SOLAR: SVR12 in GT1 or 4 With Decompensated Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>LDV/SOF + RBV 12 wks</th>
<th>LDV/SOF + RBV 24 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTP B (GT 1)</td>
<td>26/30 (87%)</td>
<td>20/23 (87%)</td>
</tr>
<tr>
<td>CTP C (GT 4)</td>
<td>24/27 (89%)</td>
<td>22/23 (96%)</td>
</tr>
</tbody>
</table>

SOLAR-2: Change in MELD Score From BL to FU Wk 4 in CPT B or C Disease

Pre/Posttransplantation (CPT B and C; n = 136)*

Change in MELD Score

-10 * (11)
-8 ** (-17)
-6
-4
-2
0
2
4

n = 18


Dosing Considerations for Pts With Renal Impairment

- **OBV/PTV/RTV + DSV**: no dose adjustment required with mild, moderate, or severe renal impairment (CrCl: ≥ 15 mL/min)[1,2]

- **LDV/SOF and SMV + SOF**: no dose adjustment required with mild or moderate renal impairment (CrCl ≥ 30 mL/min)[3,4]
  - Safety and efficacy not established in severe renal impairment or hemodialysis
  - TARGET data demonstrate feasibility of SOF-containing regimens but renal and urinary AEs increased across decreasing eGFR strata[5]

- **DCV**: no dose adjustment required with any degree of renal impairment (studied in subjects with CrCl: ≥ 15 mL/min)[6]

- **RBV**: dose adjustment required for CrCl < 50 mL/min[7]

<table>
<thead>
<tr>
<th>CrCl</th>
<th>RBV Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-50 mL/min</td>
<td>Alternating 200 mg and 400 mg every other day</td>
</tr>
<tr>
<td>&lt; 30 mL/min</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>200 mg/day</td>
</tr>
</tbody>
</table>

Hepatitis B
Initial Evaluation and Tests to Diagnose HBV
**HBV Screening Algorithm**

1. **Assess HBsAg**
   - **Positive**
     - Acute HB or CHB*
     - Evaluate for treatment
   - **Negative**
     - Assess anti-HBs
       - **Negative** (no antibodies)
         - Vaccinate
       - **Positive** (antibodies present)
         - Immune to HBV

*Time from positive HBsAg test to diagnosis of CHB is 6 mos.

Hepatitis B Serology: First Phase Testing

- Total anti-HBc can be used as alternative; those testing positive should be tested for HBsAg and anti-HBs
  - Appears at the onset of symptoms in acute hepatitis and persists for life
  - Presence indicates **EXPOSURE** (previous or ongoing infection with HBV)

Hepatitis B Serology: IgM anti-HBc

- IgM anti-HBc (IgM antibody to hepatitis B core antigen)[1]
  - Presence indicates acute infection (negative in chronic infection)
    - Positivity indicates recent infection with HBV (≤ 6 mos)
    - Occurs in the presence of acute exacerbation of chronic HBV disease

**Interpretation of Serologic Results**

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Total Anti-HBc</th>
<th>IgM Anti-HBc</th>
<th>Anti-HBs</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
<td>Negative</td>
<td>Susceptible; offer vaccination</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>NA</td>
<td>Positive</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>NA</td>
<td>Positive</td>
<td>Immune due to hepatitis B vaccination</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Chronic HBV infection</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Acute HBV infection/ Reactivation of Chronic HBV Infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>NA</td>
<td>Negative</td>
<td>Unclear; could be any one of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. Resolved infection (most common)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. False-positive anti-HBc; susceptible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. “Low-level” chronic infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4. Resolving acute infection</td>
</tr>
</tbody>
</table>

Case 1: Acute Hepatitis B, non-severe

- 54 yo Caucasian female
- RUQ pain, nausea, fatigue
- Multiple sexual partners
- ALT 1,520 IU/mL, AST 1,230 IU/mL, ALP 220 IU/mL, Bilirubin 3.2 mg/dL, INR 1.0, Platelets 265,000/mm3
- HBsAg +, Anti-HBs -, Anti-HBc IgM +, Anti-HCV -
- HBeAg +, HBV DNA 365,000 IU/mL
- U/S: Hepatomegaly, no splenomegaly, no ascites, thickened GB wall, normal bile ducts
Case 1: Acute Hepatitis B, severe

- 54 yo Caucasian female
- RUQ pain, nausea, fatigue, has noticed worsening jaundice 1 week ago
- Multiple sexual partners
- ALT 1,520 IU/mL, AST 1,230 IU/mL, ALP 220 IU/mL, Bilirubin 17.2 mg/dL, INR 1.8, Platelets 265,000/mm3
- HBsAg +, Anti-HBs -, Anti-HBc IgM +, Anti-HCV -
- HBeAg +, HBV DNA 365,000 IU/mL
- U/S: Hepatomegaly, no splenomegaly, no ascites, thickened GB wall, normal bile ducts
Acute Hepatitis B

Treat only if severe, prevent acute liver failure

Severe:
- significant coagulopathy (INR > 1.5)
- prolonged high bilirubin (>4 weeks >10)

Definition of acute liver failure:

Acute severe impairment of liver function with icterus and coagulopathy

No underlying chronic liver disease

Hepatic Encephalopathy
Assessing Patients with chronic hepatitis B for Treatment Candidacy: To Treat or Not to Treat?
## Phases of Chronic HBV Infection

<table>
<thead>
<tr>
<th>Immune Tolerance</th>
<th>Immune Clearance</th>
<th>Low Replicative Phase</th>
<th>Reactivation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg+</strong></td>
<td><strong>HBeAg-/anti-HBe+</strong> (precore/core promoter variants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$2 \times 10^8$ -</td>
<td>$2 \times 10^{11}$ IU/mL</td>
<td>$&lt; 2000$ IU/mL</td>
<td>$&gt; 2000$ IU/mL</td>
</tr>
<tr>
<td>$2 \times 10^{10}$ IU/mL</td>
<td>$200,000 - 2 \times 10^9$ IU/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/mild CH</td>
<td>Moderate/severe CH</td>
<td>Normal/mild CH</td>
<td>Moderate/severe CH</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Inactive cirrhosis</td>
<td>Inactive-carrier state</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td><strong>HBeAg+</strong> chronic hepatitis</td>
<td><strong>Inactive-carrier state</strong></td>
<td><strong>HBeAg-</strong> chronic hepatitis</td>
<td></td>
</tr>
</tbody>
</table>

Slide courtesy of A. S. F. Lok, MD.
Natural History of HBV: Directly Related to HBV DNA Level

*HBV is the 6th leading cause of liver transplantation in the United States.

Who Should Be Treated?

- Not a question of who to treat, but when: treat now or monitor and treat later when indicated
- All HBV carriers are potential treatment candidates
- A patient who is not a treatment candidate now can be a treatment candidate in the future
  - Changes in HBV replication status and/or activity/stage of liver disease
  - Availability of new or improved treatments
## Determining Treatment Candidacy for Chronic Hepatitis B: Guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>HBeAg Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA, IU/mL</td>
<td>ALT</td>
</tr>
<tr>
<td>AASLD 2009[1]</td>
<td>&gt; 20,000</td>
<td>&gt; 2 x ULN or positive biopsy*</td>
</tr>
<tr>
<td>APASL 2008[3]</td>
<td>≥ 20,000</td>
<td>&gt; 2 x ULN</td>
</tr>
<tr>
<td>NIH Consensus Conference 2009[4]</td>
<td>&gt; 20,000</td>
<td>&gt; 2 x ULN or positive biopsy*</td>
</tr>
</tbody>
</table>

*Moderate/severe inflammation or significant fibrosis.

- Expert guidelines also published with recommendations specific for HBV management in US[5] and more recently for Asian Americans[6]
  - Some key differences between these guidelines

HBV Treatment Landscape in 2015

- Interferon alfa-2b
- Lamivudine
- Peginterferon alfa-2a
- Entecavir
- Adefovir
- Tenofovir
- Telbivudine
Current Guideline Recommendations for First-line Therapy

- Peginterferon alfa-2a
- Entecavir
- Tenofovir

5-Yr Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients

*Telbivudine rate determined at Yr 2.

Selection of Entecavir vs Tenofovir: Either Is an Excellent Choice for Most Patients

- **Log HBV DNA ↓ at Wk 48-52**
  - HBeAg positive: Entecavir 6.9 vs Tenofovir 6.2
  - HBeAg negative: Entecavir 5.0 vs Tenofovir 4.6

- **Genotypic resistance, %**
  - NA naive: Entecavir 1.2 (Yr 5) vs Tenofovir 0 (Yr 3)
  - Lamivudine experienced: Entecavir 51 (Yr 5) vs Tenofovir NR

- **Pregnancy rating**
  - Class C vs Class B

- **AEs**
  - Entecavir: None
  - Tenofovir: Renal toxicity; ↓ BMD