Clearing the Confusion: Lab Testing in the Diagnosis and Management of Viral Hepatitis

April 12, 2011

Welcome

Your Host: Karen Riba

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• Questions will be answered at the end of the presentation

Welcome

Dr. Katherine Soreng, Ph.D.

Dr. Soreng received her BSc in Biology from the University of Washington in Seattle. She was awarded a Ph.D. in Immunology and Molecular Pathogenesis from Emory University in Atlanta, GA, publishing a thesis on protein synthesis and cytoskeletal elements in the Class II restricted processing of antigen.

Speaker Information

Learning Objectives

At the end of this presentation participants will be able to:
• Identify the appropriate tests involved in the differential diagnosis of viral hepatitis (including acute vs chronic)
• Discuss the algorithms useful for both hepatitis B and C antibody test confirmation
• Discuss the clinical utility of viral load and genotype in both hepatitis B and C infection.

Disclosures

Full-time employee of Siemens Healthcare
Sr. Manager of Clinical Education and Scientific Publications
Clearing the Confusion: Lab Testing in the Diagnosis and Management of Viral Hepatitis

Stages of Liver Damage

- Normal
- Liver injury/inflammation
- Liver fibrosis
- Liver failure/liver cancer

Physical Symptoms Of Liver Failure

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Bleeding/bruising easily</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Swollen abdomen/legs</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Intense skin itching</td>
</tr>
<tr>
<td>Clay stool, dark urine, tenderness</td>
<td>Mental disorientation</td>
</tr>
</tbody>
</table>

Introduction

“The beginning of health is to know the disease”

Chinese proverb

Common Causes of Hepatitis

- Metabolic Disease
- Bacteria
- Viruses
- Alcohol
- Drugs

Acute Hepatitis Symptoms

- Mouth & Upper GI Tract
- Lower Digestive Tract
- Arm & Leg Joints & Muscles
- Fever
- Jaundice

Common Tests for Identifying Liver Disease

- Is there liver injury?
- What is causing the damage?
- ALT
- AST
- Alkaline phosphatase
- LDH
- Total bilirubin
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Common Types of Viral Hepatitis

- Hepatitis A
- Hepatitis E
- Hepatitis D
- Hepatitis B
- Hepatitis C

Viral Hepatitis - Overview

<table>
<thead>
<tr>
<th>Type of Hepatitis</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Source of virus</td>
<td>feces</td>
<td>blood-derived body fluids</td>
<td>blood-derived body fluids</td>
<td>blood-derived body fluids</td>
<td>feces</td>
</tr>
<tr>
<td>Route of transmission</td>
<td>fecal-oral</td>
<td>percutaneous permucosal</td>
<td>percutaneous permucosal</td>
<td>percutaneous permucosal</td>
<td>fecal-oral</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Prevention</td>
<td>pre/post-exposure immunization</td>
<td>pre/post-exposure immunization</td>
<td>blood donor screening; risk behavior modification</td>
<td>pre/post-exposure immunization; risk behavior modification</td>
<td>ensure safe drinking water</td>
</tr>
</tbody>
</table>

Acute vs. Chronic Viral Hepatitis

- Liver damage
- Death
- Progression
- Fulminant
- HAV
- HBV
- HEV
- HCV
- Chronic
- Stable disease
- Recovery
- Time
- 6 months

HAV: Severity

- Usually mild, most recover
- Frequently symptomless, especially in children
- May be sick for several months
- Can cause acute liver failure and death
- Patient populations with the greatest risk for significant disease include:
  - Persons 50 years of age or older
  - Persons with other liver diseases, such as hepatitis B or C.

HAV Serological Course

- Fecal HAV shedding
- Total anti-HAV
- Resolution and immunity
- ALT
- anti-HAV IgM

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HAV Serological Tests

- **Anti-HAV IgM**
  - Indicates acute infection
  - Can be detected in blood about 3-4 weeks after infection
  - IgM antibodies not generally detectable within 3-12 months

- **Anti-HAV-Total**
  - Detects both IgM and IgG
  - Positive in acute and recovered hepatitis
  - Present in infected and vaccinated populations

HAV Transmission Risk Factors

- Birth (spread from an infected mother to her baby during birth)
- Sex with an infected partner
- Sharing needles, syringes, or other drug-injection equipment
- Sharing items such as razors or toothbrushes with an infected person
- Direct contact with the blood or open sores of an infected person
  - Exposure to blood from needlesticks or other sharp instruments

HBV Transmission

- **High Viral Titer**
  - Blood
  - Serum
  - Wound exudates

- **Moderate Viral Titer**
  - Semen
  - Vaginal fluid
  - Saliva

- **Low Viral Titer**
  - Urine
  - Feces
  - Sweat
  - Tears
  - Breast milk

HBV Transmission Risk Factors

- Birth (spread from an infected mother to her baby during birth)
- Sex with an infected partner
- Sharing needles, syringes, or other drug-injection equipment
- Sharing items such as razors or toothbrushes with an infected person
- Direct contact with the blood or open sores of an infected person
  - Exposure to blood from needlesticks or other sharp instruments

HBV Infection Outcomes in Adults

- **Acute HBV**
  - Subclinical infection
  - HBsAg carrier ~5%
  - Fulminant hepatitis

- **Recovery immunity ~95%**
- Chronic hepatitis
- Asymptomatic HBsAg carrier

- **Liver injury**
- **Liver cirrhosis**

- **Liver cancer**

HBV Infection Outcomes in Newborns

- **Acute HBV**
  - Subclinical infection
  - HBsAg carrier ~90%
  - Fulminant hepatitis

- **Clinical infection**
  - HBsAg carrier ~10%

- Chronic hepatitis
- Asymptomatic HBsAg carrier

- **Liver injury**
- **Liver cirrhosis**

- **Liver cancer**

- **Death**
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Chronic HBV Correlates Inversely with Age

<table>
<thead>
<tr>
<th>Age at Infection</th>
<th>Chronicity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months</td>
<td>90-95</td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>80</td>
</tr>
<tr>
<td>1-4 years</td>
<td>30-50</td>
</tr>
<tr>
<td>&gt;4 years</td>
<td>5-10</td>
</tr>
</tbody>
</table>

Immunoprophylaxis to Prevent Perinatal Transmission

<table>
<thead>
<tr>
<th>Vaccine Dose and HBIG*</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Vaccine Dose</td>
<td>Birth (within 12 hrs)</td>
</tr>
<tr>
<td>HBIG</td>
<td>Birth (within 12 hrs)</td>
</tr>
<tr>
<td>Second Vaccine Dose</td>
<td>1 - 2 months</td>
</tr>
<tr>
<td>Third Vaccine Dose</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Infant Born to Mother Not Screened for HBsAg

<table>
<thead>
<tr>
<th>Vaccine Dose</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Vaccine Dose</td>
<td>Birth (within 12 hrs)</td>
</tr>
<tr>
<td>HBIG</td>
<td>Screen mother ASAP. If HBsAg positive, give ASAP but by no later than 1 week of age</td>
</tr>
<tr>
<td>Second Vaccine Dose</td>
<td>1 - 2 months</td>
</tr>
<tr>
<td>Third Vaccine Dose</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Hepatitis B Virus Structure

- Envelope
- Nucleocapsid (core antigen)
- Viral DNA
- Surface antigens
- HBe Antigen

Hepatitis B Testing

- Serology
  - Manual and automated methods are available to identify antibody to or antigen from the Hepatitis B virus
- Molecular Tests
  - Detect viral load for therapeutic decision making

Serological Tests For HBV

- Antibody detection
- Antigen detection
- Anti-HBs
- Anti-HBc IgM
- Anti-HBe
- Anti-HBc total
- HBsAg
- HBeAg

HBV Serological Profile:
Acute Infection with Recovery

- Symptoms
- Titer: HBeAg, Anti-HBe
- Weeks after exposure
- Total anti-HBc
  - HBsAg
  - Anti-HBc IgM
  - 5%-HBs
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**HBV Serological Profile:**

**Chronic “Non-replicative” Infection**

<table>
<thead>
<tr>
<th>Weeks after exposure</th>
<th>Titer</th>
<th>HBsAg</th>
<th>HBeAg</th>
<th>anti-HBe</th>
<th>anti-HBc IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
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<td>52</td>
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<td>0</td>
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<tr>
<td>100</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Chronic non-replicative state**

- Titer: 1
- HBsAg: 1
- HBeAg: 0
- anti-HBe: 0
- anti-HBc IgM: 0
- anti-HBs rarely seen

**Chronic replicative state**

- Titer: 1
- HBsAg: 1
- HBeAg: 1
- anti-HBe: 1
- anti-HBc IgM: 1
- anti-HBs rarely seen

**Hepatitis B Testing**

<table>
<thead>
<tr>
<th>Probable Diagnosis</th>
<th>Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected, unvaccinated</td>
<td>HBsAg, anti-HBcT, anti-HBc IgM, HBeAg, anti-HBe, anti-HBs</td>
</tr>
<tr>
<td>Vaccinated (immune)</td>
<td>HBsAg, anti-HBcT, anti-HBc IgM, HBeAg, anti-HBe, anti-HBs</td>
</tr>
<tr>
<td>Acute infection</td>
<td>HBsAg, HBeAg, anti-HBc IgM, anti-HBe, anti-HBs</td>
</tr>
<tr>
<td>Active infection: recovering</td>
<td>HBsAg, HBeAg, anti-HBc IgM, anti-HBe, anti-HBs</td>
</tr>
<tr>
<td>Recovered (immune)</td>
<td>HBsAg, HBeAg, anti-HBc IgM, anti-HBe, anti-HBs</td>
</tr>
<tr>
<td>Chronic replicative infection</td>
<td>HBsAg, HBeAg, anti-HBc IgM, anti-HBe, anti-HBs</td>
</tr>
<tr>
<td>Chronic nonreplicative infection</td>
<td>HBsAg, HBeAg, anti-HBc IgM, anti-HBe, anti-HBs</td>
</tr>
</tbody>
</table>

**Treating Chronic HBV**

- Treatment options include: Telbivudine, Interferon Alpha, Pegylated interferon, Entecavir, Lamivudine, Adefovir, Telbivudine.
- Treatment is often lifelong - few are cured.

**Treatment Goals for Chronic HBV**

- Chronic replicative state
  - Titer: 1
  - HBsAg: 1
  - HBeAg: 1
  - anti-HBe: 1
  - anti-HBc IgM: 1
  - anti-HBs rarely seen

- Chronic non-replicative state
  - Titer: 1
  - HBsAg: 1
  - HBeAg: 0
  - anti-HBe: 0
  - anti-HBc IgM: 0
  - anti-HBs rarely seen

**Guidelines for treatment**

- IASLD Issues Updated Practice Guidelines for Management of Chronic Hepatitis B

  **Summary**
  The American Association for the Study of Liver Diseases (AASLD) published a revised version of its Practice Guidelines for Management of Chronic Hepatitis B in the September 2019 issue of Hepatology. Key changes are new recommendations for first- and second-line oral antivirals, reflecting the latest research on hepatitis B virus (HBV) treatment and the recent approval of telbivudine (Telristo) for this indication.

  The current revision is the fourth version of the guidelines, which were last updated in 2007, since the last revision, the U.S. Food and Drug Administration (FDA) has approved telbivudine for treatment of chronic hepatitis B, in addition to its previous indications for liver disease.
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Hepatitis C

HCV Prevalence

HCV Infection In The US

HCV Transmission

HCV: “The Silent Epidemic”

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Stage</td>
<td>Symptoms rare (~20%) and generalized</td>
</tr>
<tr>
<td>Late Stage</td>
<td>Symptoms still rare (nausea, jaundice, fatigue)</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>Often 20-30 years post-exposure</td>
</tr>
<tr>
<td>Initial ID of</td>
<td>Elevated liver enzyme profiles (AST, ALT)</td>
</tr>
<tr>
<td>Damage</td>
<td></td>
</tr>
<tr>
<td>Transmission</td>
<td>Infected individuals may unknowingly spread virus</td>
</tr>
<tr>
<td>Disease</td>
<td>Chronicity &gt;75%-80%</td>
</tr>
</tbody>
</table>
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Lab Testing in the Diagnosis and Management of Viral Hepatitis

Although IV Drug Abuse Is The Leading Risk, Other Causes Of HCV Include:
- Tattoos
- Occupational hazards
- Manicure and pedicure

Another Risk - Going to a Clinic?!

Hepatitis C Virus (HCV)

HCV RNA Genome

2nd or 3rd generation HCV IA detects antibody to 3 or more viral proteins

HCV Infection Testing Algorithm

RIBA for HCV antibody confirmation

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>IgG Control Level II</th>
<th>c100(p)</th>
<th>S-1-1(p)</th>
<th>c33c</th>
<th>c22 (p)</th>
<th>NS5</th>
<th>hSOD</th>
<th>IgG Control Level I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Indeterminate</td>
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<tr>
<td>Indeterminate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
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**HCV Progression**

<table>
<thead>
<tr>
<th>Time after exposure</th>
<th>Symptoms</th>
<th>AbHCV/RIBA</th>
<th>ALT/AST</th>
<th>Genotype and Viral Load</th>
<th>Liver Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>±</td>
<td>Normal</td>
<td>Other tests</td>
<td>Genotyping Assay</td>
<td>Other tests</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td></td>
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<tr>
<td>4</td>
<td></td>
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</tr>
</tbody>
</table>

**Testing of the HCV Infected Patient**

- Has the patient ever been infected? → Anti-HCV serology
- How much virus is present? → Viral Load
- What genotype is the patient infected with? → Genotyping Assay
- Is the patient responding to therapy? → Viral Load/Qualitative assay
- Is the patient relapsing? → Viral Load/Qualitative assay

**Technologies to detect HCV RNA include:**

- RT-PCR
- bDNA
- TMA
- Line Probe Assay (LiPA)

**Technologies to detect HCV genotype include:**

- RT-PCR with sequencing
- Line Probe Assay (LiPA)

**Molecular Testing in Treatment of HCV Patients**

- Pegylated interferon
- Ribavirin

Therapy response varies with genotype and compliance.
## Treatment of HCV

### NIH Guidelines

**Management of Hepatitis C 2002**

NIH Consensus Conference Statement

- **Baseline:** Quantitative & Genotype
- **Week 12:** Quantitative
  - `<2 log10 drop`
  - `≥2 log10 drop`

**Stopping Rules**

- **EVR:** Early Virologic Response
- **RVR:** Rapid Virologic Response
- **SVR:** Sustained Virologic Response

**HCV Treatment Algorithm**

1. **Baseline:** Quantitative & Genotype
2. **Week 12:** Quantitative
   - `<2 log10 drop`
   - `≥2 log10 drop`
3. **Genotype 1:** 48 weeks
4. **Genotype non-1:** 24 weeks
5. **End treatment, Qualitative:**
   - 6 month follow-up, Qualitative

**Non-responder**
- HCV RNA (+)
- HCV RNA Relapsers
- HCV RNA Non-responder

**Sustained responder**
- HCV RNA (-)

---

### Side Effects of HCV Therapy

<table>
<thead>
<tr>
<th>Pegylated interferon</th>
<th>Ribavirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropsychiatric</strong></td>
<td></td>
</tr>
<tr>
<td>Depression, anxiety, irritability, fatigue</td>
<td>Cough and dyspnea</td>
</tr>
<tr>
<td>Bone marrow depression</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Anorexia / weight loss</td>
<td>Teratogenicity</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Exacerbation of autoimmune disorders</td>
<td>Rash / Puritus</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>Nausea</td>
</tr>
</tbody>
</table>

- **Teratogenicity**
- **Rash / Puritus**
- **Thyroid dysfunction**
- **Alopecia**

### Management of Hepatitis C: 2002

NIH Consensus Conference Statement

- A minimum 2 log decrease in viral load during the first 12 weeks of treatment
- Predictive of SVR and should be a routine part of monitoring patients
SVR vs. Non-Response (NR) to the Anti-Viral Therapies*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SVR (%)</th>
<th>NR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN mono</td>
<td>15%</td>
<td>85%</td>
</tr>
<tr>
<td>IFN + RBV</td>
<td>41%</td>
<td>59%</td>
</tr>
<tr>
<td>Peg + RBV</td>
<td>56%</td>
<td>44%</td>
</tr>
<tr>
<td>Peg + RBV (80/80/80)</td>
<td>63%</td>
<td>37%</td>
</tr>
</tbody>
</table>


Outcome with PEG-IFN α2a +R: 12 Week Stopping Rule

Outcome with PEG-IFN α2b +R: 12 Week Stopping Rule

Therapeutic Response: RVR

RVR in the 2009 AASLD HCV
Time to Undetectability Predicts SVR

Using RVR in patient management

6 HCV Genotypes and > 50 Subtypes

HCV Genotypes can Predict Treatment Success

HCV Treatment: Genotypes Make a Difference

HCV - HIV Coinfection
**Clearing the Confusion:**
**Lab Testing in the Diagnosis and Management of Viral Hepatitis**

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**HCV Mono-infected vs HCV-HIV Co-infected Patients**

![Graph showing treatment with Pegylated Interferon + Ribavirin](image)

**Patient Presentation**

Nausea, slight fever, hepatomegaly, jaundice

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**Acute Viral Hepatitis Testing Panel**

<table>
<thead>
<tr>
<th>HAV IgM</th>
<th>HBsAg</th>
<th>HBV Core IgM</th>
<th>Anti-HCV</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Acute HAV</td>
</tr>
<tr>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>HCV-acute, chronic, resolved?</td>
</tr>
<tr>
<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>Chronic HBV?</td>
</tr>
<tr>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Acute HBV?</td>
</tr>
</tbody>
</table>

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**Resources**

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- American Association for the Study of Liver Disease (AASLD) – [www.aasld.org](http://www.aasld.org)
- Diagnosis, Management and Treatment of Hepatitis C: An Update – [www.aasld.org](http://www.aasld.org)

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**Thank-you for Attending**

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This webinar has been recorded and will be available by April 14th, on [www.paml.com](http://www.paml.com), under the Hospital Tab/Hospital Portal/Webinar Series heading. 

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