Ortho Clinical Diagnostics

The ABCs of Viral Hepatitis

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Objectives

• Define viral hepatitis
• Discuss various types of viral hepatitis
• Explain clinically useful diagnostic tests
• Describe CDC guidelines for hepatitis screening
• Examine the differences in available Hepatitis C assays
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Hepatitis Overview
What is Viral Hepatitis?

- Hepatitis is a viral infection that causes inflammation of the liver
- There are five main types of hepatitis: A, B, C, D, E
- Approximately 3.5–5.3 million Americans living with viral hepatitis, and most of them do not know that they are infected.
- Hepatitis B and C can lead to chronic disease in hundreds of millions of people, are the most common cause of liver cirrhosis and cancer
- About 1 million people die each year from causes related to viral hepatitis
- A safe and effective vaccine can prevent hepatitis A and B infection

Source: CDC.gov/hepatitis
Clinical Features of Viral Hepatitis

Symptoms common to most forms of hepatitis include:

- Flu-like symptoms - fatigue
- Fever
- Headache
- Nausea
- Muscle aches or pain
- Jaundice
Acute versus Chronic Hepatitis

Acute
• First time infection (symptomatic or asymptomatic) which is cleared by the body in less than six months

Chronic
• The disease last longer than six months

Acute hepatitis can resolve totally or go on to a chronic state
## Types of Viral Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Types of Hepatitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of virus</td>
<td>Feces</td>
<td>Blood/blood derived body fluids</td>
<td>Blood/blood derived body fluids</td>
</tr>
<tr>
<td>Route of transmission</td>
<td>Fecal-oral</td>
<td>Percutaneous permucosal</td>
<td>Percutaneous permucosal</td>
</tr>
<tr>
<td>Chronic Infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</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>
</tr>
</tbody>
</table>

Source: CDC.gov/hepatitis
Current Vaccines

Hepatitis A

• There is currently a vaccine
  • Given in two doses – initial and a booster at least six months apart from the initial dose

Hepatitis B

• There is currently a vaccine
  • Three dose series

Hepatitis C

• There is no vaccine
Hepatitis A
Hepatitis A Overview

- Small, single stranded RNA virus
- In 2013, 1,781 cases reported in U.S.
- Routes of transmission are typically (fecal – oral) through:
  - Close person to person contact
  - Ingestion of contaminated food or water
- Individuals at risk include:
  - Those in close contact with infected person
  - Injecting and non-injecting drug users
  - Daycare centers, travelers, military
Incidence of Hepatitis A

Incidence of hepatitis A, by year United States, 1980-2013

Source: CDC.gov/hepatitis
Hepatitis A Clinical Course

Source: CDC.gov/hepatitis
Laboratory Diagnosis of HAV

- Acute infection is diagnosed by detection of HAV-IgM
- Total anti-HAV antibody is used as a marker of past infection
  - Measures IgG and IgM HAV antibodies
  - IgG long lasting and confers immunity
Hepatitis B
Hepatitis B Overview

- Consists of partly double stranded DNA virus
- Four major serotypes, adr, adw, ayr, ayw, and eight genotypes (A–H)
- Estimated cases in the United States up to 40,000/year
- In the U.S.: 1.4 to 2 million Americans are living with chronic HBV infection (vs. 900,000 living with HIV/AIDS)
  - More than 50% with chronic HBV infections are of Asian or Pacific Islander descent.
- Without early diagnosis or intervention, 1 in 4 of those with chronic HBV infection will develop liver cancer or experience liver failure
- About 2 billion people have been infected with HBV; 600,000 people die each year due to the consequences of hepatitis B
Incidence of Hepatitis B

Incidence of hepatitis B, by year United States, 1980-2013

Source: CDC.gov/hepatitis
Transmission of HBV

- Sexual contact
- Blood-to-blood contact by unsafe injecting practices
- Blood transfusion
- Unsterile medical equipment
- HBV is an important occupational hazard for health workers
- Mother-to-child transmission
Perinatal Hepatitis B (HBV)

- HBV can be passed from a mother to her baby during birth (perinatal infection)
- Infants infected at birth may later experience potentially fatal complication, including cirrhosis, chronic liver disease, and liver cancer
- Infected infants have a 90% risk of chronic infection. 25% of chronically infected infants are at risk for premature death due to HBV
- Post-exposure prophylaxis (PEP) is 85-95% effective when given within 12 hours of birth to infants born with HBV
Prevention of Perinatal HBV Infection

• Begin with first dose with 12 hours of birth
• Hepatitis B vaccine (first dose) and HBIG
• Complete vaccination series at six months of age
• Test for response after completion of at least three doses of HepB series at nine through 18 months of age

New Recommendation

- Testing between nine and 12 months instead of nine and 18 months
- Provides two opportunities for clinicians to assess these infants for infection at the nine- and 12-month wellness visits
Post Vaccination Serologic Testing

- Not routinely recommended following vaccination of infants, children, adolescents, or most adults
- Recommended for:
  - Infants born to HBsAG+ women
  - Hemodialysis patients
  - Immuno deficient persons
  - Sex partners of persons with chronic HBV infection
  - Certain healthcare personnel
Acute Hepatitis B Virus Infection with Recovery Typical Serologic Course

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>HBeAg</th>
<th>anti-HBc</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>IgM anti-HBc</td>
<td>Total anti-HBc</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Titer</th>
<th>Weeks after Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>32</td>
<td>36</td>
</tr>
<tr>
<td>52</td>
<td>100</td>
</tr>
</tbody>
</table>

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Laboratory Diagnosis of HBV

- HBsAg - used as a general marker of infection
- HBsAb - used to document recovery and/or immunity to HBV infection
- Anti-HBc IgM - marker of acute infection
- Anti-HBc IgG - past or chronic infection
- HBeAg - indicates replication virus and therefore infectiveness
- Anti-HBe - virus is no longer replicating; however, the patient may still be positive for HBsAg which is made by integrated HBV
- Testing for antibodies to HBsAg (anti-HBs) and hepatitis B core antigen (anti-HBc) is also done as part of a screening panel to help distinguish between infection and immunity.
- Diagnosis of chronic HBV infection is characterized by persistence of HBsAg for at least six months
Hepatitis C
Hepatitis C Overview

- Hepatitis C virus (HCV) is an enveloped, single stranded, positive sense, RNA virus
- HCV is the most common chronic blood-borne viral infection in North America
- Major cause of chronic hepatitis
- Causes progressive hepatic fibrosis which leads to cirrhosis and an increased risk of hepatocellular carcinoma
- HVC liver disease is the most common reason for liver transplantation in USA
- Genotypes 1 (75%), 2 and 3 (20-25%) are the most common in the U.S.

Source: Viral Hepatitis Action.org
Incidence of Hepatitis C

Incidence of hepatitis C, by year United States, 1980-2013

Source: CDC.gov/hepatitis
Transmission of HCV

Transmission of HCV is mainly parenteral routes primarily transmitted through contaminated

- Blood and blood products
- Intravenous drug use (IDU)
- Contaminated medical equipment
- Tattoos
- Human body secretions
CDC HCV Infection and Testing Guidance

Hepatitis C Guidance Time Line

1998
- CDC recommendations for persons with risks for HCV infection

2003
- CDC published guidelines for Laboratory Testing and result reporting of antibody to HCV

2012
- CDC amended testing recommendation to include one-time HCV testing for all persons born during 1945-1965 regardless of risk factors

2013

Source: CDC
Why Screen for HCV in People Born from 1945 to 1965 (Baby Boomers)

• Approximately 75% of the estimated 3.2 million people chronically infected with hepatitis C were born during 1945-1965, or are Baby Boomers.

• National prevalence data show that people born during these years are five times more likely than other adults to be infected.

• Hepatitis C is a leading cause of liver cancer and the leading cause of liver transplants.

• People born during 1945-1965 account for 73% of all hepatitis C-associated mortality.
Testing for HCV Infection – An Update

Reasons for 2013 Update

• Changes in the availability of certain HCV antibody tests

• Evidence that many persons who are identified as reactive by an HCV antibody test might not subsequently be evaluated to determine if they have current HCV infection

• Significant advances in the development of antiviral agents with improved efficacy against HCV
HCV Testing Recommendations

**Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection**

- **HCV antibody**
  - **Nonreactive**: No HCV antibody detected → STOP
  - **Reactive**: Not Detected → HCV RNA
    - **Not Detected**: No current HCV infection → Additional testing as appropriate
    - **Detected**: Current HCV infection → Link to care

*For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.*

†To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

HCV Antibody Tests

- HCV Elisa II or III
  - Most common antibody test
- OraQuick
  - Whole blood and fingerprick approved
- A positive antibody test indicates exposure
  - It does not indicate current hepatitis C infection
  - HCV viral load test performed to indicate active HCV infection
Genotype Test

• Why is a Genotype Test Important?
  ▪ Guide treatment, drug selection and treatment duration

• Genotype (1, 2, 3, 4, 5, and 6)
  ▪ U.S. population
    ◆ 70% genotype 1
      • Cure rate up to 95%
      • Treatment duration eight to 12 weeks
    ◆ 30% genotypes 2 and 3
      • Genotype 2-12 weeks = 93% cure rate
      • Genotype 3-24 weeks = 84% cure rate

• FDA recommends HBV testing for patients receiving direct acting therapy
### Interpretation of Results of Tests for HCV

<table>
<thead>
<tr>
<th>Test Outcome</th>
<th>Interpretation</th>
<th>Further Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV antibody nonreactive</td>
<td>No HCV antibody detected</td>
<td>• Sample can be reported as nonreactive for HCV antibody. No further action required.  &lt;br&gt;  • If recent exposure in person tested is suspected test for HCV RNA.*</td>
</tr>
<tr>
<td>HCV antibody reactive</td>
<td>Presumptive HCV infection</td>
<td>• A repeatedly reactive result is consistent with current HCV infection, or past infection that has resolved, or biologic false positivity for HCV antibody.  &lt;br&gt;  • Test for HCV RNA to identify current infection.</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA detected</td>
<td>Current HCV infection</td>
<td>• Provide person tested with appropriate counseling and link person tested to care and treatment</td>
</tr>
<tr>
<td>HCV antibody reactive, HCV RNA not detected</td>
<td>No current HCV infection</td>
<td>• No further action required in most cases.  &lt;br&gt;  • If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay.  &lt;br&gt;  • In certain situations, follow up with HCV RNA testing and appropriate counseling.</td>
</tr>
</tbody>
</table>

# Technical Specifications of Commercially Available Hepatitis C Assays

<table>
<thead>
<tr>
<th>Test</th>
<th>Test Format</th>
<th>Antigens</th>
<th>Time to results (min)</th>
<th>Sample Type</th>
<th>Sample Volume (µl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elecsys Anti-HCV</td>
<td>1-step sandwich</td>
<td>Core, NS3, NS4</td>
<td>20</td>
<td>Serum, plasma (heparin, EDTA)</td>
<td>40</td>
</tr>
<tr>
<td>Architect Anti-HCV</td>
<td>2-step sandwich</td>
<td>HCr-43, c-100-3-SOD</td>
<td>28</td>
<td>Serum, plasma (heparin, EDTA, citrate, oxalate)</td>
<td>20</td>
</tr>
<tr>
<td>ADVIA Centaur Anti-HCV</td>
<td>2-wash sandwich</td>
<td>C200, C22-3, NS5</td>
<td>41</td>
<td>Serum, plasma (heparin, EDTA)</td>
<td>10</td>
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<tr>
<td>VITROS ECi HCV</td>
<td>2-step sandwich</td>
<td>C22-3, c200, NS5</td>
<td>55</td>
<td>Serum, plasma (heparin, EDTA, citrate)</td>
<td>20</td>
</tr>
<tr>
<td>Prism Anti-HCV</td>
<td>2-step sandwich</td>
<td>C100-3, HCr43, NS5</td>
<td></td>
<td>Serum, plasma (EDTA, oxalate, citrate)</td>
<td>50</td>
</tr>
<tr>
<td>AxSym Anti-HCV</td>
<td>2-step sandwich</td>
<td>HCr43, c200, c100-3, NS5</td>
<td>30</td>
<td>Serum, plasma (heparin, EDTA, citrate, oxalate)</td>
<td>33</td>
</tr>
</tbody>
</table>

Hepatitis Laboratory Testing
Why Develop Testing Algorithms

• Testing algorithms are widely used in infectious disease diagnosis
• Based on the concept of simple, easily performed, inexpensive, highly sensitive screening test which is followed by a more complex, expensive but specific confirmatory test
• No single test is 100% sensitive and specific
Terms used for Reporting Tests with Uncertain Test Results

Non-definitive tests results

or

Preliminary test results include
Types of Test Results

I’m a Low Positive

I’m an Indeterminate

I’m an Equivocal

I’m a Gray Zone
What are the Consequences of Equivocal Results

• Laboratory
  - Cost of retesting – resolution of discrepancies
  - Cost of additional test – confirmatory testing

• Clinician
  - Education
  - Medical liaison
Challenges to Retesting

- Insufficient sample quantity
- Sample deterioration
- Sample-processing errors
- Loss of patients to follow-up
- Miscommunication between clinicians and patients
Questions?
Thank You