Current Concepts in Hepatitis Testing

Presented by
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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 and 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

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

Source: https://www.cdc.gov/hepatitis/index.htm
Acute versus Chronic Hepatitis

Acute
- First time infection (symptomatic or asymptomatic) which is cleared by the body in less than six months
- Acute hepatitis can resolve totally or go on to a chronic state

Chronic
- The disease last longer than six months

Source: https://www.cdc.gov/hepatitis/index.htm

Types of Viral Hepatitis

<table>
<thead>
<tr>
<th>Types of Hepatitis</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<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</td>
<td>Percutaneous</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: https://www.cdc.gov/hepatitis/index.htm

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

Source: https://www.cdc.gov/hepatitis/index.htm

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

Source: http://www.cdc.gov/hepatitis/HAV/index.htm

Incidence of Hepatitis A

Source: http://www.cdc.gov/hepatitis/HAV/index.htm
HAV Prevalence by State

HAV-Serological Course

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

Source: http://www.cdc.gov/hepatitis/HAV/index.htm

Hepatitis B

- 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
- Globally, about 2 billion people have been infected with HBV; 600,000 people die each year due to the consequences of hepatitis B

Source: https://www.cdc.gov/hepatitis/hbv/ April 2017

Incidence of Hepatitis B

Source: https://www.cdc.gov/hepatitis/hbv/ viewed April 2017
HBV Prevalence by State

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 Hepatitis B 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 well-child 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

HBV Structure
Serological Course of Acute Hepatitis B

**Acute Hepatitis B Virus Infection with Recovery**

- **Symptoms:** fever, nausea, vomiting, jaundice
- **Tests:**
  - **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:** Represents the patient response to HBeAg.
- **Diagnosis of chronic HBV infection is characterized by persistence of HBsAg for at least six months**


Hepatitis B Treatment

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Genus Name</th>
<th>Manufacturer</th>
<th>Indication</th>
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</tbody>
</table>

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 - Represents the patient response to HBeAg.
- 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.

Source: [https://www.cdc.gov/hepatitis/hbv/index.htm](https://www.cdc.gov/hepatitis/hbv/index.htm)

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
- HCV 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: CDC, National Notifiable Diseases Surveillance System (NNDSS)
Figure 4.2. Incidence of acute hepatitis C, by age group — United States, 2000–2014

Figure 4.3. Incidence of acute hepatitis C, by sex — United States, 2000–2014

Figure 4.4. Incidence of acute hepatitis C, by race/ethnicity — United States, 2000–2014

Figure 4.5. Availability of risk exposures/behaviors associated with acute hepatitis C — United States, 2014

Figure 4.6a. Acute hepatitis C reports, by risk exposure/behavior — United States, 2014

Figure 4.6b. Acute hepatitis C reports, by risk exposure/behavior — United States, 2014

Source: CDC, National Notifiable Diseases Surveillance System (NNDSS)

*Includes case reports indicating the presence of at least one of the following risks 2 weeks to 6 months prior to onset of acute hepatitis C: 1) using injection drugs; 2) having sexual contact with a suspected/confirmed hepatitis C patient; 3) being a man who has sex with men; 4) having multiple sex partners concurrently; 5) having sexual contact with a suspected/confirmed hepatitis C patient; 6) having household contact with a suspected/confirmed hepatitis C patient; 7) being a hemodialysis patient; 8) having received a blood transfusion; 9) having sustained a percutaneous injury; and 10) having undergone surgery.

†More than one risk exposure/behavior may be indicated on each case-report.

§Risk data not reported.
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

Source: [https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section2](https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section2)

HCV Prevalence by State


Serological Course of Chronic Hepatitis C

Source: [http://pathmicro.med.sc.edu/virol/hepc-cd2.jpg](http://pathmicro.med.sc.edu/virol/hepc-cd2.jpg)

CDC HCV Infection and Testing Guidance

Hepatitis C Guidance Time Line

1998

CDC recommendations for persons with risk 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


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

- Approximately 80% of the estimated 3.5 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
- Therefore, labs should expect an increase in test requests!


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 Reactive
  - Not Detected
    - No current HCV infection
    - Additional testing as appropriate†
  - Detected
    - Current HCV infection
- HCV RNA
  - No HCV antibody detected
    - STOP*

* 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.


Hepatitis C Treatment

- Higher cure rates (>90%)
  - When a patient has reached “SVR” (Sustained Virologic Response), which translated means when HCV viral load is undetectable after 6 months of treatment
- Less severe side effects
  - No anemia, depression or flu-like symptoms (as with past therapeutic approaches)

Source: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section4

HCV Antibody Tests

- HCV Elisa II or III
  - Most common antibody test
- OraQuick
  - Whole blood and finger-prick 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

Source: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#c2

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

Sources: https://www.fda.gov/forpatients/illness/hepatitisbc/ucm408658.htm (sourced April 2017)
https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#d4
http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf
**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.</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 biological false positivity for HCV antibody.</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 is required in most cases.</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>Roche Elecsys</td>
<td>1-step</td>
<td>Core, NS3, NS4</td>
<td>20</td>
<td>Serum, plasma (heparin, EDTA)</td>
<td>40</td>
</tr>
<tr>
<td>Abbott Architect</td>
<td>2-step</td>
<td>HC-43, p-100-3-500</td>
<td>28</td>
<td>Serum, plasma (heparin, EDTA, citrate, oxalate)</td>
<td>20</td>
</tr>
<tr>
<td>Siemens ADVIA Centaur</td>
<td>2-wash sandwich</td>
<td>C200, C22-3, NS5</td>
<td>41</td>
<td>Serum, plasma (heparin, EDTA)</td>
<td>10</td>
</tr>
<tr>
<td>Ortho VITROS® Immunodiagnostic System</td>
<td>2-step sandwich</td>
<td>C23-3, C25-3, NS5</td>
<td>55</td>
<td>Serum, plasma (heparin, EDTA, oxalate)</td>
<td>20</td>
</tr>
</tbody>
</table>


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**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

Source: [https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#c4](https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#c4)

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**What are the Consequences of Equivocal Results**

- Laboratory
  - Cost of retesting – resolution of discrepancies
  - Cost of additional test – confirmatory testing
- Clinician
  - Education
  - Medical liaison

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**Challenges to Retesting**

- Insufficient sample quantity
- Sample deterioration
- Sample-processing errors
- Loss of patients to follow-up
- Miscommunication between clinicians and patients
For More Information

Questions?

Thank You