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Current Concepts in Hepatitis Testing

Presented by
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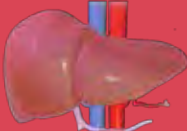
Objectives

- 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

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

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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>

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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>

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Types of Viral Hepatitis

Types of Hepatitis	A	B	C
Source of virus	Feces	Blood/blood derived body fluids	Blood/blood derived body fluids
Route of transmission	Fecal-oral	Percutaneous permucosal	Percutaneous permucosal
Chronic Infection	No	Yes	Yes
Prevention	Pre/post exposure immunization	Pre/post exposure immunization	Blood donor screening/ risk behavior modification

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

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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>

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Hepatitis A

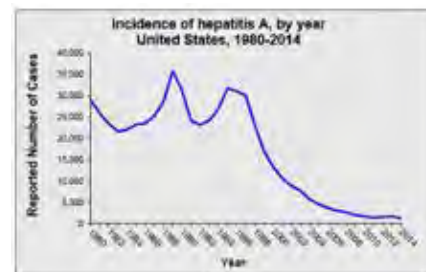
Hepatitis A Overview

- 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

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

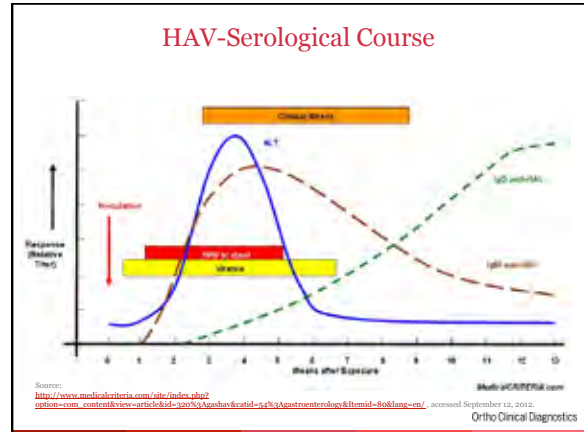
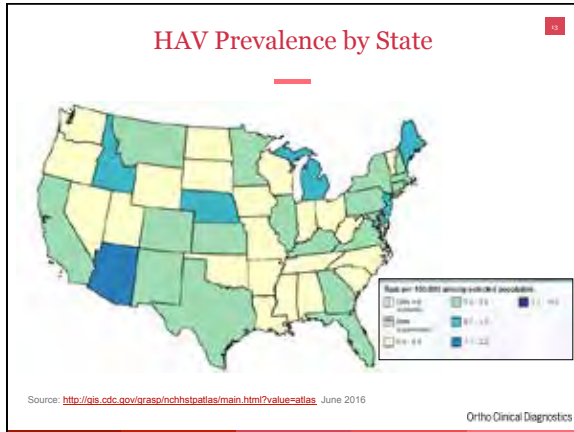
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Incidence of Hepatitis A



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

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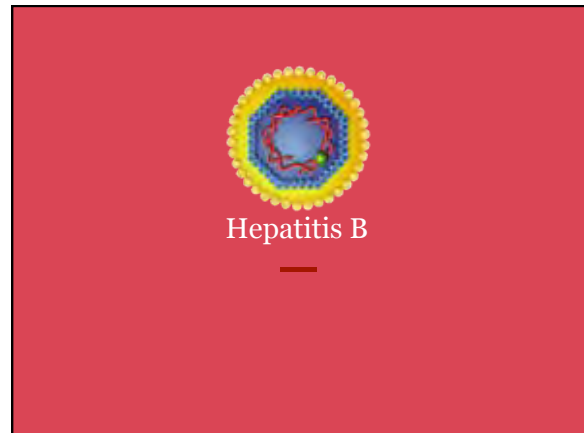


Laboratory Diagnosis of HAV

- 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>

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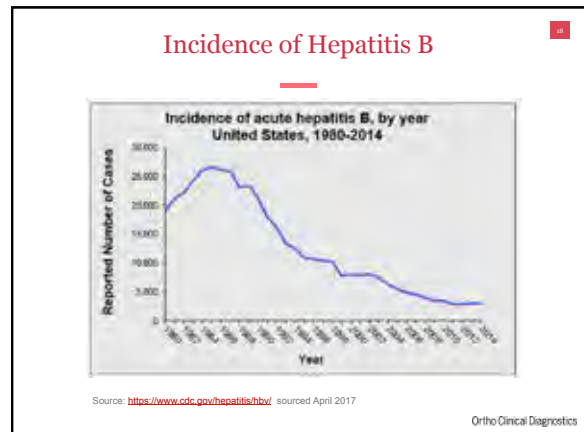


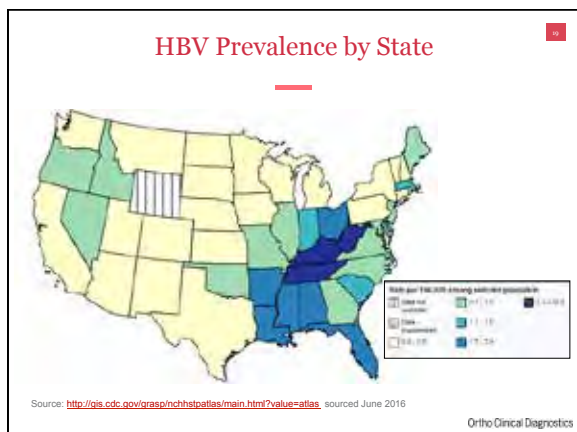
Hepatitis B Overview

- 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
- 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


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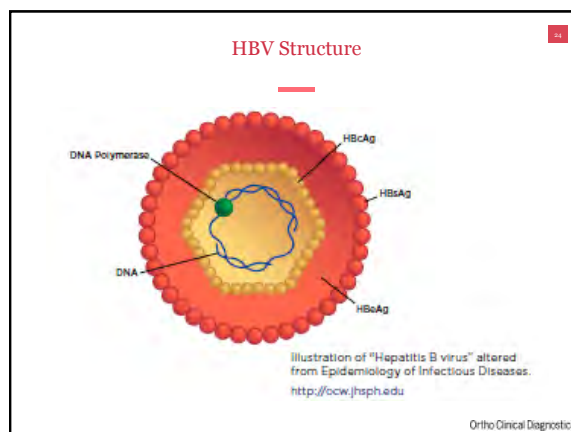


- ### Transmission of HBV
- Sexual contact
 - Blood-to-blood contact by unsafe injecting practices
 - Blood transfusion
 - Unsterile medical equipment
 - HBV is an important occupational hazard for health workers
 - Mother-to-child transmission
- Source: <https://www.cdc.gov/hepatitis/hbv/index.htm>
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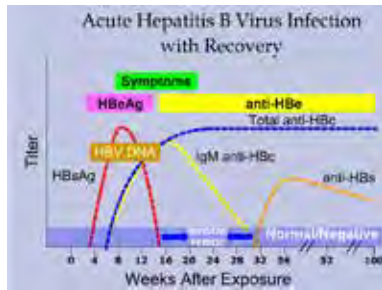
- ### Perinatal Hepatitis B (HBV)
- HBV can be passed from a mother to her baby during birth (perinatal infection)
 - Infants infected at birth may later experience potentially fatal complication, including cirrhosis, chronic liver disease, and liver cancer
 - Infected infants have a 90% risk of chronic 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
- 
- Source: <https://www.cdc.gov/hepatitis/hbv/perinatalexmin.htm> sourced April 2017
- Ortho Clinical Diagnostics

- ### 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
- 
- Source: <https://www.cdc.gov/hepatitis/hbv/perinatalexmin.htm>
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6439a6.htm?e_cid=mm6439a6_e
- Ortho Clinical Diagnostics

- ### 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
- Source: <https://www.cdc.gov/hepatitis/hbv/index.htm>
- Ortho Clinical Diagnostics



Serological Course of Acute Hepatitis B



Source: http://www.cdc.gov/hepatitis/Resources/Professionals/Training/Serology/vg_hbv_acute.htm September 2012. Ortho Clinical Diagnostics

Laboratory Diagnosis of HBV

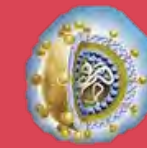
- HBsAg- used as a general marker of infection
- HBsAb- used to document recovery and/or immunity to HBV infection
- Anti-HBc IgM- marker of acute infection
- Anti-HBc IgG- past or chronic infection
- HBeAg- indicates replication virus and therefore infectiveness
- Anti-HBe- Represents the patient response 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.
- Diagnosis of chronic HBV infection is characterized by persistence of HBsAg for at least six months

Source: <https://www.cdc.gov/hepatitis/hbv/index.htm> Ortho Clinical Diagnostics

Hepatitis B Treatment

Brand Name	Generic Name	Manufacturer Name	Indication
Seroctide	interferon	Bristol Myers Squibb	chronic hepatitis B virus infection with evidence of active viral replication
Cytor HBV	tenofovir	Ciena/SmithKline	chronic hepatitis B associated with hepatitis B viral replication and active liver inflammation
Hepresso	adefovir dipivoxil	Glaxo Sciences	chronic hepatitis B in patients 18-72 years of age
Virace A	entecavir alpha-2b	Schering	chronic hepatitis B in patients 1 year of age or older with compensated liver disease
Pegayso	pegylated interferon	Roche	treatment of adult patients with HBeAg positive and HBeAg negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and liver inflammation
Tyroska	telbivudine	Novartis	chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferase (ALT or AST) or histologic ally active disease
Viralid	tenofovir	Glaxo Sciences	chronic hepatitis B in adults

Source: <https://www.fda.gov/forpatients/illness/hepatitis/b/ucm408658.htm> Ortho Clinical Diagnostics



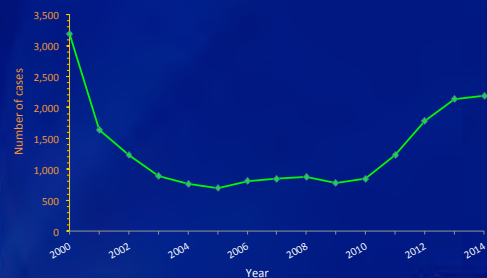
Hepatitis C

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.

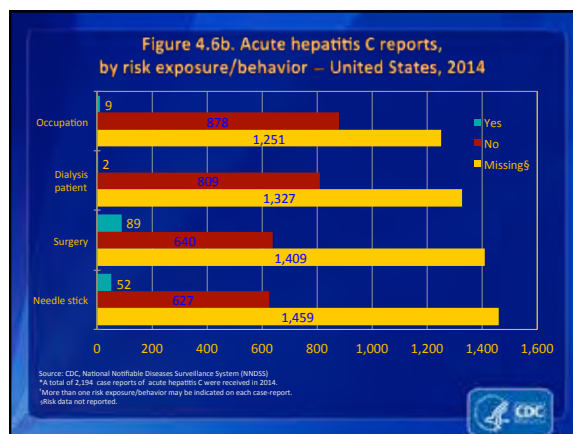
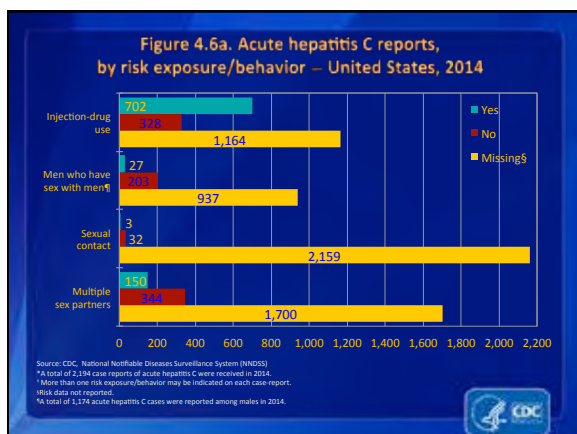
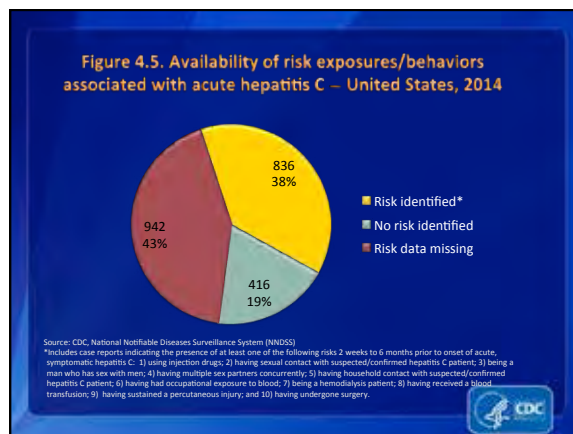
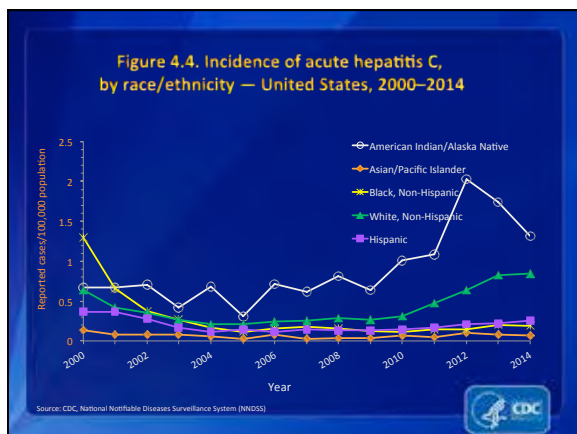
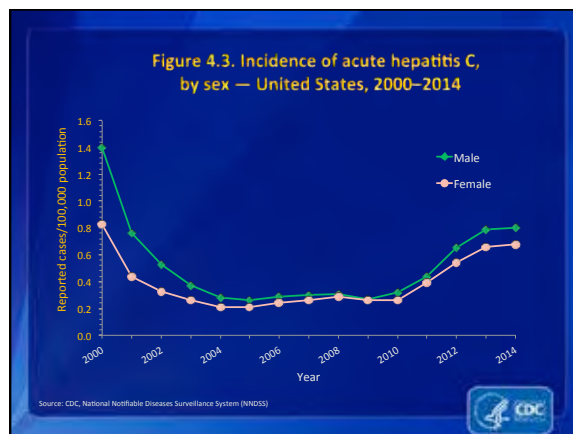
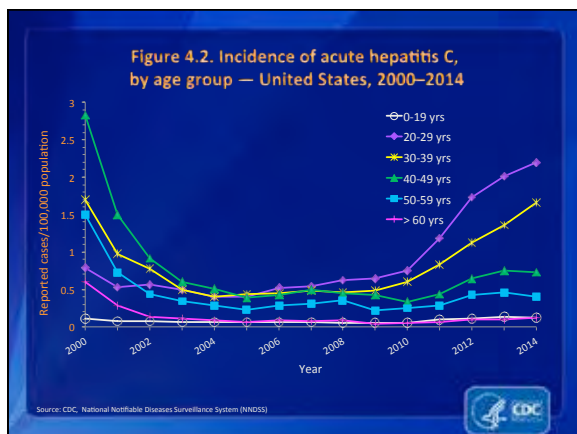
Sources: <https://www.cdc.gov/hepatitis/hcv/index.htm> <http://www.viralhepatitisaction.org/> Ortho Clinical Diagnostics

Figure 4.1. Reported number of acute hepatitis C cases — United States, 2000–2014



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





Transmission of HCV

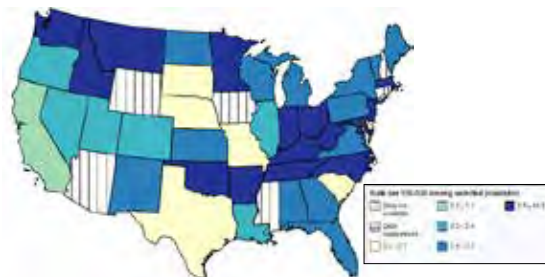
Transmission of HCV is mainly parenteral routes primarily transmitted through contaminated

- 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>

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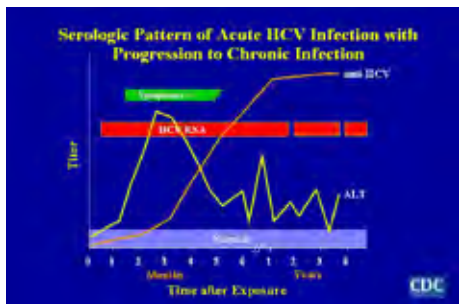
HCV Prevalence by State



Source: <http://gis.cdc.gov/grasp/ncb/states/main.htm?value=sales>, June 2016

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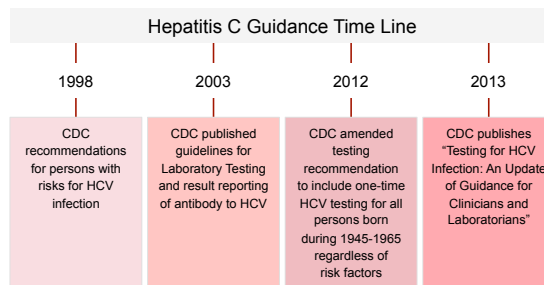
Serological Course of Chronic Hepatitis C



Source: <http://pathmicro.med.sc.edu/viral/hepc-cd2.jpg>, September 2012.

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CDC HCV Infection and Testing Guidance



Source: <http://www.cdc.gov/mmwr/pdf/mm6104.pdf>, sourced April 2017

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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!



Source: <http://www.cdc.gov/mmwr/pdf/mm6104.pdf>, sourced April 2017

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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

Source: <http://www.cdc.gov/mmwr/pdf/mm6104.pdf>, sourced April 2017

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HCV Testing Recommendations

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

```

graph TD
    A{HCV antibody} -- "+" --> B[Reactive]
    A -- "-" --> C[Non-reactive]
    C --> D[No HCV antibody detected]
    B --> E{HCV RNA}
    E -- "-" --> F[No current HCV infection]
    E -- "+" --> G[Current HCV infection]
    F --> H[Additional testing is appropriate?]
    G --> I[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.
 †In alternative panel, repeat HCV antibody test using two assays for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing for persons tested in accordance with the HCV response within the past 6 months or the clinical relevance of HCV chronicity. If there is concern regarding the sensitivity or specificity of the test, repeat.
 Source: CDC. Testing for HCV infection. Available from <http://www.cdc.gov/mmwr/pdf/tr16104.pdf>. Accessed April 2017.

Source: <http://www.cdc.gov/mmwr/pdf/tr16104.pdf> sourced April 2017

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CDC: HCV Testing for All Baby Boomers

Source: <http://www.cdc.gov/mmwr/pdf/tr16104.pdf> sourced April 2017

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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.html#section4>

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Hepatitis C Treatment

- **A new generation of FDA approved drugs**
 - OLYSIO® (Simeprevir) – a protease inhibitor (blocks specific proteins needed by HCV)
 - SOLVADI® (Sofosbuvir) – a polymerase inhibitor (blocks specific proteins produced by HCV)
 - HARVONI® (combo of Sofosbuvir & Ledipasvir) – has received considerable press & promotion
 - One pill, once a day for 12 weeks
 - Patients don't have to take ribavirin and interferon injections as in the past
 - Approved to treat genotypes 1, 4, 5 & 6

Sources: <https://www.fda.gov/forpatients/lines/hepatitisbcvcm408658.htm> (sourced April 2017)
<https://www.olyzio.com/shared/product/olyzio-prescribing-information.pdf>
http://www.gilead.com/-/media/Files/pdfs/medicines/liver-disease/solvadi/solvadi_pi.pdf
https://www.gilead.com/-/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf

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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.html#2>

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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/lines/hepatitisbcvcm408658.htm> (sourced April 2017)
<https://www.cdc.gov/hepatitis/hcv/hcvfaq.html#4>
<https://www.olyzio.com/shared/product/olyzio-prescribing-information.pdf>
http://www.gilead.com/-/media/Files/pdfs/medicines/liver-disease/solvadi/solvadi_pi.pdf
https://www.gilead.com/-/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf

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Interpretation of Results of Tests for HCV

Test Outcome	Interpretation	Further Actions
HCV antibody nonreactive	No HCV antibody detected	<ul style="list-style-type: none"> Sample can be reported as nonreactive for HCV antibody. No further action required. If recent exposure in person tested is suspected test for HCV RNA.*
HCV antibody reactive	Presumptive HCV infection	<ul style="list-style-type: none"> A repeatedly reactive result is consistent with current HCV infection, or past infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.
HCV antibody reactive, HCV RNA detected	Current HCV infection	<ul style="list-style-type: none"> Provide person tested with appropriate counseling and link person tested to care and treatment
HCV antibody reactive, HCV RNA not detected	No current HCV infection	<ul style="list-style-type: none"> No further action required in most cases. 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. In certain situations, follow up with HCV RNA testing and appropriate counseling.

Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013.62(18).

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Technical Specifications of Commercially Available Hepatitis C Assays

Test	Test Format	Antigens	Time to results (min)	Sample Type	Sample Volume (µl)
Roche Elecsys	1-step sandwich	Core, NS3, NS4	20	Serum, plasma (heparin, EDTA)	40
Abbott Architect	2-step sandwich	HCr-43, c-100-3-SOD	28	Serum, plasma (heparin, EDTA, citrate, oxalate)	20
Siemens ADVIA Centaur	2-wash sandwich	C200, C22-3, NS5	41	Serum, plasma (heparin, EDTA)	10
Ortho VITROS® 3600 Immunodiagnostic System	2-step sandwich	C22-3, c200, NS5	55	Serum, plasma (heparin, EDTA, citrate)	20

Source: Multicenter evaluation of a fully automated third generation anti-HCV antibody screening test with excellent sensitivity and specificity: Albornio, F., et al, Med Microbiol Immunol, 24 Sept 2010

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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#d4>

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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




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For More Information




Hepatitis and HIV Fast Facts

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Test	Specimen	Turnaround Time	Reference Range	Interpretation
Hepatitis A (Anti-HAV IgG)	Serum	2-3 weeks	Positive	Indicates past or current infection
Hepatitis B (Anti-HBc)	Serum	2-3 weeks	Positive	Indicates past or current infection
Hepatitis C (Anti-HCV)	Serum	2-3 weeks	Positive	Indicates past or current infection
HIV-1 (Anti-HIV-1)	Serum	2-3 weeks	Positive	Indicates past or current infection


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Questions?

Thank You

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