

Recommendations and Guidelines for Hepatitis C Virus Screening and Testing

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Faculty

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Objectives

- Explain transmission and prevention of Hepatitis C virus (HCV)
- Explain general function of the liver
- Discuss transmission routes
- Define HCV antibody and HCV RNA testing options
- Discuss symptoms of HCV
- Explain HCV testing sequence
- Discuss importance of disease management and reasons to pursue treatment

Introduction and Outline

- Basics of liver function and injury
- Virology of Hepatitis C virus
- Natural history and clinical illness of HCV
- Epidemiology of HCV in the U.S.
- Rationale for therapy
- At-risk groups and testing recommendations

Introduction and Outline

- Testing methods and diagnosis of HCV infection
- Linkage to care and disease management

Overview of Hepatic Function

- Manufacturing blood proteins that aid in clotting, oxygen transport, and immune system function
- Storing excess nutrients and returning some of the nutrients to the bloodstream
- Manufacturing bile, a substance needed to help digest food

Overview of Hepatic Function

- Helping the body store glucose in the form of glycogen
- Ridding the body of toxins in the bloodstream, including drugs and alcohol
- Breaking down saturated fat and producing cholesterol

What is Hepatitis?

- “Liver inflammation”
- Based on biochemical or clinical findings
- Many possible causes:
 - Alcohol or other toxins
 - Genetic disorders

What is Hepatitis?

- Non - alcoholic fatty liver disease (NAFL and NASH)
- Autoimmune disease
- Metabolic storage diseases
- Medications
- Viruses or other infectious agents

Viral Hepatitis

- Alphabet Soup (acute and / or chronic)
 - HAV
 - HBV
 - HCV
 - HDV
 - HEV



Viral Hepatitis

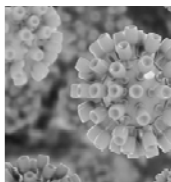
- Other viruses (acute)
 - EBV
 - CMV
 - VZV

Hepatitis C Virus

- A major cause of “non-A, non-B” hepatitis
- Single - stranded RNA virus that infects hepatocytes
- Identified in 1989
- Transmitted through blood and body fluids
- Infects only some primates

Hepatitis C Virus

- Can live outside body for several hours (perhaps a few days?)
- No vaccine
- Many different “strains,” known as genotypes



HCV Genotypes

- 6 major genotypes, and more than 50 subtypes
- Genotype 1 is most common in U.S. and worldwide (60 – 75% of cases)
- Major implications for therapy
- Distinct geographic distribution of genotypes

Acute HCV Infection

- Most patients are asymptomatic
- When symptoms are present, they develop 2 – 26 weeks after exposure, typically about 7 – 8 weeks later
- Patients may have jaundice, nausea, right upper quadrant pain, and dark urine, with symptoms lasting 2 – 12 weeks

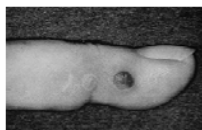
Acute HCV Infection

- Typically have elevated liver function tests, often 10 – 20 x/normal



Chronic HCV Infection

- Usually asymptomatic
- May report fatigue or other nonspecific symptoms
- May be related to certain chronic diseases
 - Mixed cryoglobulinemia
 - Renal diseases, including membranoproliferative glomerulonephritis
 - Diabetes



HCV Natural History

- Between 45 – 85 % of infected persons will develop chronic infection
- Some people will clear infection spontaneously, usually within 12 weeks
- More likely to clear spontaneously if...
 - Female sex
 - Younger age

HCV Natural History

- Symptomatic infection
- The CC allele of IL-28B gene (also more likely to respond to therapy)
- Non - black race

Hepatic Injury and Regeneration

- Liver injury from HCV, other chronic infections, toxic exposures or other factors can lead to chronic hepatitis, and may produce cellular injury, inflammation, fibrosis or cirrhosis



Hepatic Cirrhosis

- Occurs in about “20% at 20 years”
- Estimated 1 million persons with cirrhosis in mid-2020s
- Possibly a more rapid progression in HCV than other causes of cirrhosis
- Risk factors for progression of fibrosis include:

Hepatic Cirrhosis

- Alcohol use, marijuana use, co-infection with HIV or HBV, diabetes, obesity all increase risk of fibrosis / cirrhosis
- Female sex, acquisition at younger age, regular coffee consumption all decrease risk

Hepatic Cirrhosis

- Portal hypertension
 - Splenomegaly
 - Ascites
 - Varices
 - Hemorrhoids
- Decreased synthetic function
 - Bleeding tendency

Hepatic Cirrhosis

- Nutritional abnormalities
- Constitutional symptoms
 - Weakness, malaise, fatigue
- Hepatocellular carcinoma in up to 3% per year

HCV and Survival

- Up to 15,000 deaths per year estimated to occur in the U.S. from chronic HCV infection
- Age - adjusted mortality rates are higher for HCV (4.6 deaths per 100,000 persons per year) than for HIV (4.2)
- HCV patients have estimated mortality rate 12 times the general population

HCV and Survival

- As of 2007, number of deaths from HCV exceeded number from HIV
- Median age of death in HCV patients is 60 year old, compared with 78 year old in persons without HCV or HIV
- Deaths are not always directly related to HCV

Epidemiology of HCV

- About 17,000 new cases per year in the United States, a decline since the 1980s:
 - BUT, INCREASING in persons under the age of 30 years
- Leading cause of liver transplants in the United States

Epidemiology of HCV

- About 2.7 – 3.9 million persons in the U.S. with chronic HCV, and three-fourths were born between 1945 – 1965
- Worldwide, highest prevalence in the Mid-East, north Africa, and east and central Asia

Risk Factors for HCV Infection

- Intravenous drug use – odds ratio 49.6
- Blood transfusion – odds ratio 10.9
- Sex with an intravenous drug user – odds ratio 6.3
- Having been in jail more than three days – odds ratio 2.9
- Religious scarification – odds ratio 2.8

Risk Factors for HCV Infection

- Having been struck or cut with a bloody object – odds ratio 2.1
- Pierced ears or body parts – odds ratio 2.0
- Immunoglobulin injection – odds ratio 1.6

Murphy EL, et al. NHLBI Retrovirus Epidemiology Donor Study (REDS). *Hepatology* 2000; 31:756.

Risk Factors for HCV Infection

- **Injection drug use**
 - The most efficient route of transmission!
 - Frequent outbreaks in drug users
 - Many countries report that over 80% of all IDU are HCV(+)

Risk Factors for HCV Infection

- **Blood Transfusion**
 - “Non - A, non - B hepatitis”
 - Marked decline after the institution of screening for risk factors

HCV and Sexual Transmission

- **Definitely occurs but not frequently**
- **Sex is not an efficient route of transmission, more common in MSM**
- **Multiple studies put risk of HCV transmission to sexual partner at less than 1% per year**

HCV and Sexual Transmission

- **Higher risk if partner is HIV co - infected**
- **Most (but not all) public health agencies do NOT recommend condoms for discordant monogamous couples**

Costs of HCV

- **HCV - infected patients are more likely than HCV - negatives to have**
 - Higher rates of hospitalization
 - Higher prescription drug costs (about \$100,000 per course of treatment)
 - Greater chance of short-term and long-term disability

Rationale for Diagnosis and Therapy

- **About 50% of HCV - infected persons in U.S. are unaware of diagnosis**
- **Largest cohort of at - risk persons (born 1945 - 1965) is approaching age of potential complications**
- **Curative therapy is available and well - tolerated**
- **Can prevent development of cirrhosis, cancer or need for transplant**

Whom To Screen for HCV?

- Identifiable risk factor
 - IDU, occupational exposure
- High - prevalence groups
 - Incarcerated, hemodialysis patients, HIV
- Elevated liver function studies
- 1945 – 1965 birth cohort
(this recommendation added in 2012)

CDC Testing Recommendations

- Persons born from 1945 - 1965
- Persons who have ever injected illegal drugs, including those who injected only once many years ago
- Recipients of clotting factor concentrates made before 1987
- Recipients of blood transfusions or solid organ transplants before July 1992

CDC Testing Recommendations

- Patients who have ever received long - term hemodialysis treatment
- Persons with known exposures to HCV, such as:
 - Health care workers after needle sticks involving HCV - positive blood
 - Recipients of blood or organs from a donor who later tested HCV-positive

CDC Testing Recommendations

- All persons with HIV infection
- Patients with signs or symptoms of liver disease (e.g., abnormal liver enzyme tests)
- Children born to HCV - positive mothers (to avoid detecting maternal antibody, these children should not be tested before age 18 months)

<http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1>

CDC Testing Recommendations

- Need for testing is uncertain for the following:
 - Recipients of transplanted tissue after 1992
 - Intranasal cocaine or other non-injecting illicit drug users
 - Those with a history of tattooing, body piercing

CDC Testing Recommendations

- Those with a history of sexually transmitted diseases or multiple sex partners
- Long - term steady sexual partners of HCV - positive persons
- Normal LFTs do not exclude HCV infection

CDC Testing Recommendations

- Test those with other diseases that are seen with HCV
 - Mixed cryoglobulinemia

Other Testing Recommendations

- National Institutes of Health (NIH) also includes recommendations to test the following:
 - Received a blood transfusion or organ transplantation prior to 1990 (rather than 1992)
 - Have had multiple sexual partners

Other Testing Recommendations

- Are spouses or household contacts of HCV-infected patients
- Share instruments for intranasal cocaine use
- Incarcerated individuals

Testing Methods and Diagnosis of HCV Infection

- Two types of HCV tests
 - Serologic assay to detect antibodies to HCV
 - Provides evidence of whether someone has EVER been infected with HCV

Testing Methods and Diagnosis of HCV Infection

- Molecular assays to detect or quantify HCV RNA
 - Provides evidence on recent infection or of chronic HCV hepatitis

HCV Serologic Tests

- Measure serum antibodies to HCV
- Typically used for initial screening
- Does not distinguish between current and past (resolved) HCV infection
- Most commonly - used test is EIA (enzyme immunoassay)

HCV Serologic Tests

- Also available is Ora-Quick HCV Rapid Test, for initial HCV screening
- Recombinant immunoblot assay (RIBA) no longer available in U.S.

HCV Molecular Assays

- Detect nucleic acid of HCV in the serum
- Positive HCV RNA testing confirms active infection
- Can be qualitative or quantitative
- Can use HCV viral load to make decisions about therapy

How to Interpret HCV Test Results

Interpretation of Test Results for HCV Infection and Further Actions		
Test Outcome	Interpretation	Further Action
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 HCV 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 HCV 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 medical 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.

* If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.

† It is recommended before initiating antiviral therapy to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.

‡ If the person tested is suspected of having 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.

Implications of a Negative Anti-HCV Antibody Test and a Negative HCV RNA Test

- Your patient is not currently infected with HCV or is in the early "window period" between infection and the appearance of anti-HCV antibodies or RNA.

Implications of a Positive Anti-HCV Antibody Test and a Negative HCV RNA Test

- Your patient is not currently infected with HCV
 - Message for the patient:
 - You previously had an HCV infection that was cleared
 - Spontaneous clearance during acute HCV infection
 - More common in patients with the IL28B CC genotype and those not also infected with HIV
 - Clearance as the result of successful HCV treatment
 - If you engaged in activities that put you at risk for HCV infection in the past 6 months, you should be tested again for HCV RNA at least 6 months after your last potential exposure
 - You can be reinfected with HCV if you engage in risk behaviors that are associated with HCV transmission; if you are engaging in these behaviors, HCV RNA testing should be repeated at regular intervals. You will continue to have HCV antibodies for a prolonged period of time and repeat antibody testing will not be of benefit to you

Implications of a Positive Anti-HCV Antibody Test and a Positive HCV RNA Test

- Your patient is currently infected with HCV
 - Message for the patient:
 - You are currently infected with HCV
 - You need to be evaluated to understand the severity of your liver disease and to be counseled about how not to accelerate the damage the virus may be doing to your liver
 - You should be tested for other infections like HBV and HIV that may be transmitted in the same ways as HCV
 - You may benefit from certain vaccinations such as those for HBV and HAV
 - You can transmit the virus to other people
 - HCV can be successfully treated with HCV medications
 - With successful treatment, your viral infection will be cured
 - Your liver disease will stop progressing although you may need to be followed for certain complications of HCV infection

Implications of a Negative Anti-HCV Antibody Test and a Positive HCV RNA Test

• Possibilities

- Your patient is in the “window period” in the first 6–12 weeks of HCV infection. HCV RNA appears in the blood before HCV antibodies develop
 - If acute HCV infection is suspected, an urgent referral to a practitioner with expertise in treating HCV infection is appropriate because the virus is particularly responsive to therapy within the first 6 months of infection
- Your patient is immunocompromised and is not making detectable antibodies to HCV despite an active HCV infection
 - This is much less common with second and third generation anti-HCV antibody tests but it can occasionally occur in immunocompromised patients, including those with advanced HIV infection or those on dialysis

New Diagnosis of Hepatitis C Infection: Post-Test Counseling Messages

Persons infected with HCV can benefit from the following messages

- **Contact a health-care provider (either a primary-care clinician or specialist [e.g., in hepatology, gastroenterology, or infectious disease]), for**
 - medical evaluation of the presence or development of chronic liver disease;
 - advice on possible treatment options and strategies; and
 - advice on how to monitor liver health, even if treatment is not recommended.
- **Protect the liver from further harm by,**
 - considering hepatitis A and B vaccination if susceptible and if liver disease is present;
 - reducing or discontinuing alcohol consumption;
 - avoiding new medicines, including over-the-counter and herbal agents, without first checking with their health-care provider; and
 - obtaining HIV risk assessment and testing.
- **For persons who are overweight (BMI $\geq 25\text{kg/m}^2$) or obese (BMI $\geq 30\text{kg/m}^2$),**
 - consider weight management or losing weight and
 - follow a healthy diet and stay physically active.
- **To minimize the risk for transmission to others,**
 - do not donate blood, tissue, or semen and
 - do not share appliances that might come into contact with blood, such as toothbrushes, dental appliances, razors, and nail clippers.

Which one of the following most accurately describes the indication for routine hepatitis C testing in relation to injection drug use?

- 1. Indicated if the person ever injected illegal drugs**
- 2. Indicated if the person injected illegal drugs more than 10 times**
- 3. Indicated if the person injected illegal drugs for more than 1 year**
- 4. Indicated if the person injected illegal drugs for more than 3 years**

Which one of the following most accurately describes the 2012 CDC recommendation for birth cohort hepatitis C testing?

- 1. Perform one-time HCV testing for all persons 45 – 65 years of age**
- 2. Perform annual HCV testing on all persons born from 1945 – 1965**
- 3. Perform one-time HCV testing on all persons born from 1945 – 1965**
- 4. Perform annual HCV testing on all persons born from 1950 – 1970**

Which one of the following medical conditions is considered an indication for routine HCV screening?

1. Insulin - requiring diabetes mellitus
2. Renal failure on chronic hemodialysis
3. Chronic anemia
4. History of hepatitis A infection

A 57-year-old woman comes into a clinic for a routine medical visit. She undergoes testing for HCV and has a positive HCV enzyme immunoassay (EIA) test. What would you recommend as the next step?

1. Repeat the HCV EIA test
2. Perform a quantitative HCV RNA assay
3. Refer her to a hepatitis C specialist
4. No further treatment is necessary