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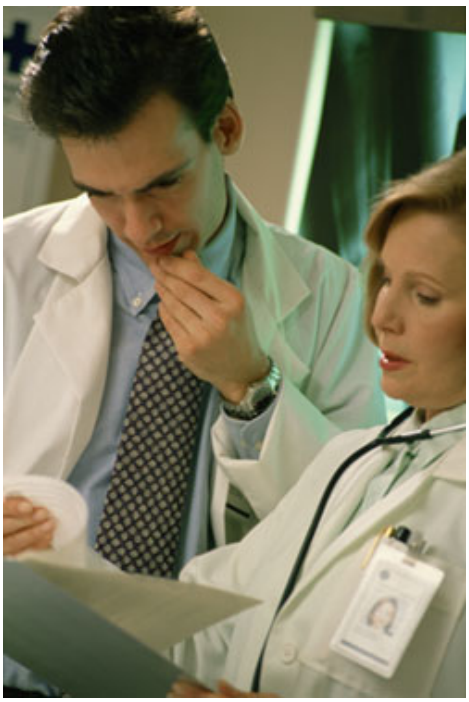

Diagnosing and Managing Hepatitis C

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Hepatitis C virus (HCV), most commonly contracted through sharing contaminated needles and syringes, is the most prevalent bloodborne infection in the United States. Almost 2% of adults in the United States are infected with HCV, and infection levels are now highest in people in their late 40s. While new infections are declining steadily, the prevalence of liver disease caused by HCV is still rising due to the time lag between the onset of infection and clinical manifestations.

Because there aren't enough specialists to care for everyone with HCV, much of the care for these patients is shifting to primary care providers. Therefore, primary care providers need to be able to screen, diagnose, and care for HCV-infected patients, and to recognize which patients should be referred to a specialist.

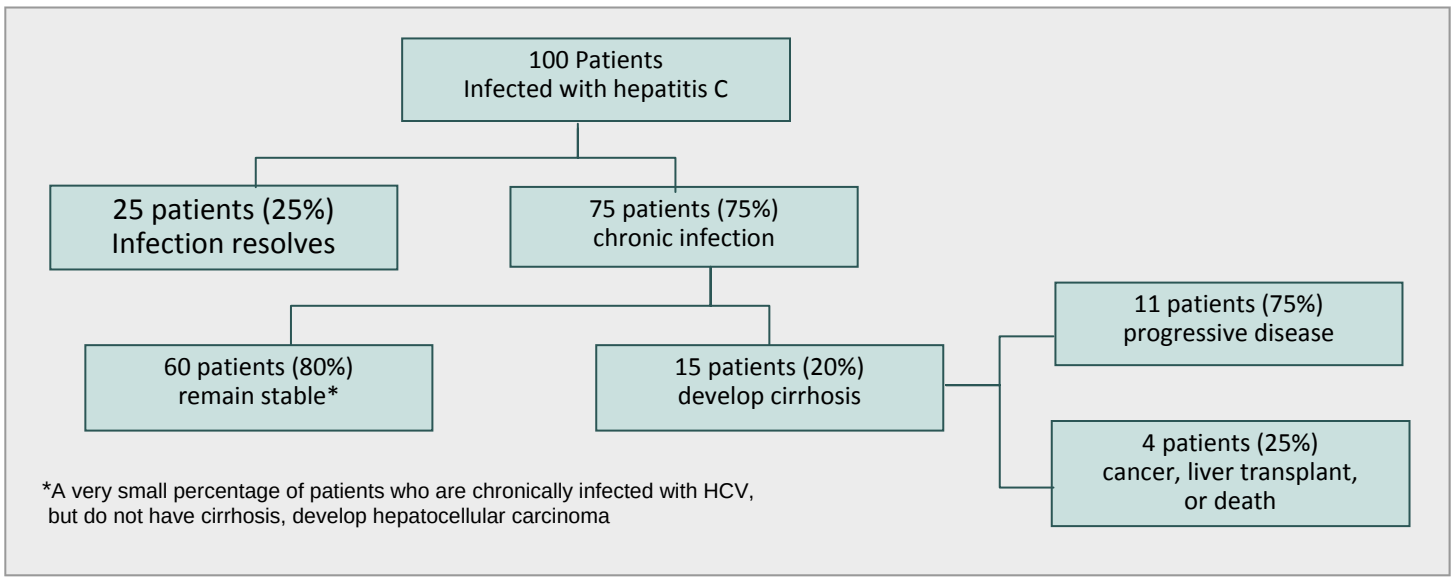
Clinical Features and Natural History

Acute infection: Most people with acute HCV infection are asymptomatic or have a mild clinical illness. Symptoms of acute infection, which may last for 2 to 12 weeks, include fatigue, nausea, and abdominal pain. Jaundice occurs in less than 25% of acutely infected patients. Approximately 70% of patients have hepatitis C antibody (anti-HCV) within 12 weeks of onset of symptoms.

About 75% of infected persons develop chronic infection; of these, approximately 80% remain asymptomatic but have persistently abnormal or fluctuating alanine aminotransferase (ALT) levels. The remaining 20% will develop cirrhosis over the next 20 to 30 years. Up to 25% of individuals who develop cirrhosis will develop hepatocellular carcinoma (HCC). Once cirrhosis is established, HCC develops at a rate of 1% to 4% per year (Figure 1).

Association with other diseases: HCV infection is associated with many extrahepatic manifestations (Table 1). Because HCV infection may not be suspected for several years, providers should be alert to the possibility of HCV infection in patients with these conditions and should ask about HCV risk factors.

FIGURE 1: HEPATITIS C VIRUS INFECTION



Screening Recommendations

Nearly a third of primary care providers are not testing patients with clearly identified risk factors for HCV (Table 2). **Providers should ask patients about risk factors for HCV and should offer testing for patients at high-risk of infection.** Testing is *not* necessary for the general population, pregnant women, non-sexual household contacts of persons infected with HCV, or healthcare workers without evidence of exposure. **All patients with HCV exposure or infection should be tested for HIV, and all patients with HIV exposure or infection should be tested for HCV.** Providers may also wish to screen some patients with risk factors for HCV who have not yet been clearly established, especially if these persons ask to be tested. These less well-identified risk factors include intranasal cocaine use, a history of tattoos, body piercing, and sexual contact with HCV-infected persons. Providers must carefully evaluate potential risk factors to guide testing decisions.

TABLE 1: EXTRAHEPATIC MANIFESTATIONS OF HEPATITIS C INFECTION

Autoimmune disorders • Idiopathic thrombocytopenic purpura • Hypothyroidism	***Renal disorders*** • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis
Dermatologic disorders • Leukocytoclastic vasculitis • Lichen planus • Porphyria cutanea tarda	***Ophthalmologic disorders*** • Corneal ulcers • Scleritis • Uveitis
Hematologic disorders • B cell non-Hodgkin's lymphoma • Essential mixed cryoglobulinemia • Monoclonal gammopathies	***Neurological disorders*** • Neuropathy

TABLE 2: INDICATIONS FOR SCREENING FOR HEPATITIS C INFECTION

- Persons who ever injected illicit drugs, even once many years ago
- Persons with HIV
- Certain recipients of transfusions or organ/tissue transplants, including:
  - Persons who received blood from a donor who later tested positive for HCV
  - Persons who received a transfusion of blood or blood products before July 1992
  - Persons who received an organ transplant before July 1992
  - Persons who received immune globulin products before December 1994
  - Persons who were ever on hemodialysis
- Children born to mothers infected with HCV
- Healthcare workers or others after percutaneous or mucosal exposure to HCV-infected blood
- Persons with persistently elevated ALT levels or other evidence of liver disease

HCV Testing and Follow-up Management

Patients at high risk for HCV should be tested by their primary care providers for anti-HCV using the enzyme immunosorbent/enzyme-linked immunoassay (EIA/ELISA) test. Providers should be aware that there are high rates of both false positive and false negative results among certain patient populations (Table 3). Additionally, a positive antibody test result only informs the provider that the patient has been exposed to HCV but cannot distinguish among acute, chronic, or resolved infections. (Figure 2 provides a summary of laboratory diagnostic tests and suggested sequences for testing.)

TABLE 3: TYPES OF TESTS AVAILABLE TO ASSESS HCV INFECTION

Detects the presence of antibody (anti-HCV)	EIA/ELISA SIGNAL TO CUTOFF RATIO(S C/O), RIBA	Ordered first to screen for HCV infection All positive tests must be confirmed with a signal to cutoff ratio (S C/0), RIBA, or qualitative RNA test High false negative rates occur in patients with immunosuppression, and new infection if pts. Have not yet developed antibodies to the virus High false positive rates occur in patients with underlying autoimmune disease or low-risk status
Detects the presence of virus (patient is infected with HCV if either type of test is positive)	Qualitative—detects HCV RNA in the blood using amplification techniques such as PCR or TMA Quantitative—measures quantity of HCV RNA in the blood using either PCR or TMA	This test is more sensitive than quantitative tests and detects virus presence as early as 1-2 weeks post-exposure. Intermittent viremia may cause a false negative result. Changes in the HCV RNA level are used to monitor treatment response; is important to obtain the viral level prior to starting treatment, and to use the same test to monitor response to therapy. It is not as sensitive as qualitative tests and should not be used to exclude the diagnosis of HCV infection

The provider should order a *qualitative* viral RNA test if the patient tests positive for HCV antibody, or if the patient may have early infection, HIV, or is otherwise immunocompromised. Qualitative viral RNA tests are more sensitive than the quantitative tests and should be used to confirm infection. Providers should not use qualitative testing as the initial HCV screening test because antibody testing is more cost effective. Qualitative test results help determine if the patient has cleared the infection (Table 4).

TABLE 4: INTERPRETATION OF TEST RESULTS

EIA/ELISA	RIBA or S C/O	QUALITATIVE TEST	INTERPRETATION
--	--	Undetectable	No past or present infection
++	--	Undetectable	False positive EIA/ELISA, no past or present infection
++	++	Undetectable	Probable past exposure with clearance of infection. Repeat qualitative RNA in 6 months to exclude fluctuating low levels of viremia
++	++	Detectable	Current infection
--	--	Detectable	Acute infection OR current infection in an immunocompromised person

Quantitative viral RNA tests measure the amount of the virus in the blood and are used to assess the likelihood of response to treatment. Low viral load is associated with a better treatment response. Levels are checked during pharmacologic therapy to monitor treatment response. This test should only be ordered for patients if treatment is not contraindicated (Table 5).

TABLE 5: CONTRAINDICATIONS TO THERAPY

Uncontrolled, major depressive disorder	Men who are sexual partners of women who are currently pregnant
Transplant recipient: kidney, heart or lung	Unwilling or unable to comply with adequate contraception
Decompensated cirrhosis	Less than 3 years old
Untreated hyperthyroidism	Known hypersensitivity to drugs used to treat HCV
Pregnancy	Unwilling or unable to comply with adequate contraception
Autoimmune hepatitis	Severe concurrent diseases (e.g., severe hypertension, poorly controlled diabetes)
Severe anemia	Any condition known to be exacerbated by interferon or ribavirin

Counseling

Providers need to discuss HCV prevention before and after testing and regardless of test results. Providers also need to clarify how HCV is transmitted and how to avoid future exposures (Table 6).

FIGURE 2: HEPATITIS C VIRUS DIAGNOSTIC TESTING ALGORITHM

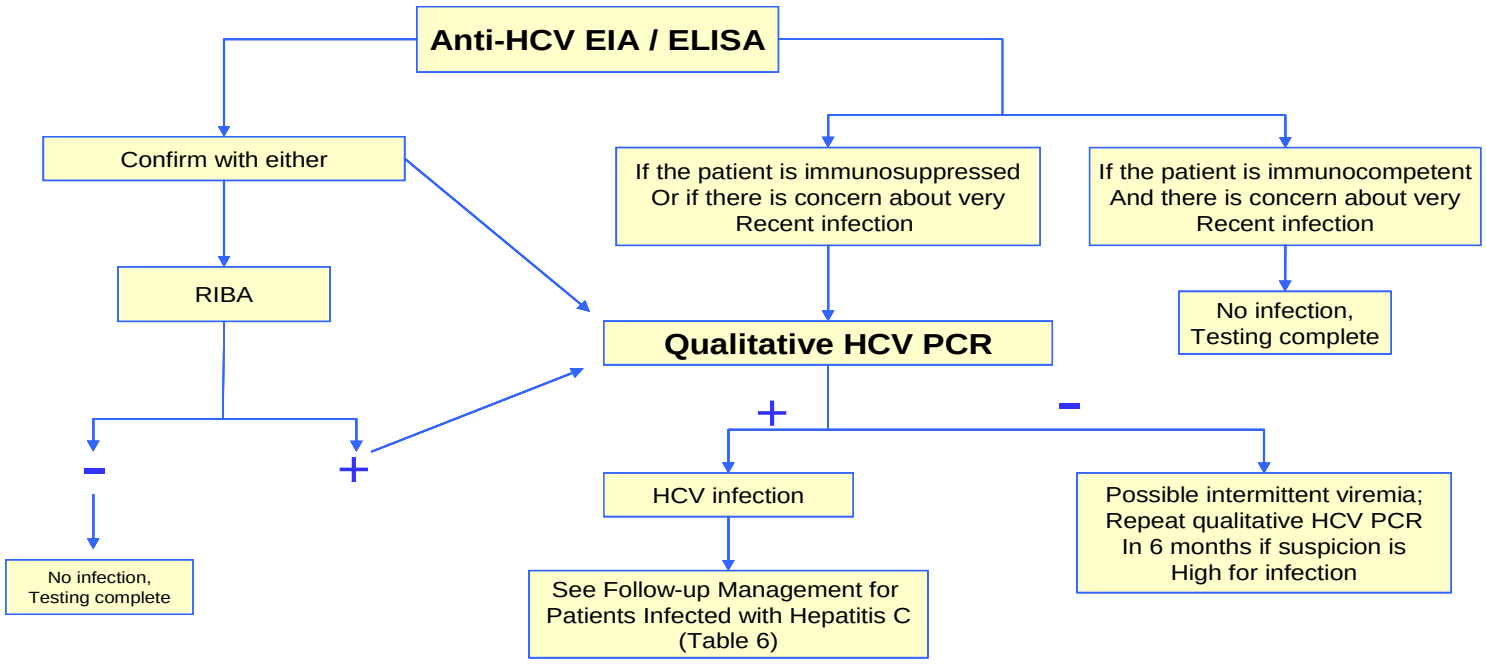


TABLE 6: WHAT TO TELL PATIENTS ABOUT HEPATITIS C

ALL PATIENTS: HCV TRANSMISSION AND PREVENTION	PATIENTS WITH HCV INFECTION: ADDITIONAL INFORMATION
HCV is transmitted through direct blood contact. Any activity that lets one person's blood come into contact with another's can transmit HCV.	Eliminate or reduce alcohol consumption (or decrease amount if unwilling or unable to stop drinking).
There is no vaccine to prevent HCV.	Do not donate blood, organs, tissue or semen.
Do not inject street drugs (Table 9). The most common way to get HCV is by injecting street drugs.	Get tested and vaccinated against hepatitis A and B.
Do not share your drug equipment if you do inject.	Get tested for HIV.
Do not share personal care items that might have blood on them (e.g., razors, toothbrushes).	Talk to your doctor before taking any new medications, including over-the-counter (e.g., Tylenol) and herbal medicines.
Only get tattoos or body piercing by a licensed tattoo artist who uses a new needle and ink pot for each client	Discuss with your sex partner the low, but not absent risk of transmitting HCV infection. If you want to lower the small chance of spreading HCV to your partner, you may decide to use barrier precautions such as latex condoms.
HCV can be spread by sex, but this is rare. If you are having sex with more than one partner, use latex condoms correctly and every time to prevent the spread of STDs.	There is no evidence on whether or not HCV infection can be spread through oral sex.

Referring Patients to a Specialist

When a patient is diagnosed with chronic HCV infection, the primary care provider should take the steps outlined in Table 7. These steps include counseling, further diagnostic and screening tests, and vaccination. Patients with chronic HCV infection who have no contraindications to therapy and would like to be considered for treatment should be referred to either a gastroenterologist or an infectious diseases specialist. If primary care providers are aware of the most current pharmacologic recommendations and feel comfortable managing the patient, they may initiate therapy. In addition, primary care providers should also refer patients with decompensating liver disease, varices, ascites, encephalopathy, and those coinfected with HBV, HIV, or another disease that may adversely affect the liver. Approximately 10-25% of HCV-infected patients are coinfected with HIV. Patients coinfected with HCV and HIV are at risk for rapid progression to liver damage, and many HIV medications can cause liver injury.

Genotype predicts the likelihood of treatment response. The decision to pursue therapy is based, in part, on knowing the genotype. There are 6 major genotypes. Type 1 is the most prevalent type in the United States and is less likely to respond to current available treatment. Types 2 and 3 have a higher likelihood of response to treatment.

The role of a liver biopsy in the management of HCV remains controversial. Liver biopsy reveals the extent of fibrosis caused by chronic infection. The extent of fibrosis is used to predict progression of disease; thus, the damage revealed by biopsy is used to determine the urgency of treatment. Deaths due to complications of liver biopsy occur in about 1 per every 10,000 procedures.

TABLE 7: FOLLOW-UP MANAGEMENT FOR PATIENTS INFECTED WITH HCV

Counsel patients on: - Preventing transmission of HCV (Table 6) - Avoiding alcohol - Avoiding hepatotoxic medications	**Order the following tests:** - Baseline liver transaminases, INR, urinalysis and albumin - Hepatitis A and B antibody tests and hepatitis B surface antigen to determine patient immunity - Hepatitis C genotype - Liver sonogram to assess for cirrhosis. If patient has cirrhosis, check alpha-fetoprotein level to evaluate risk for hepaocellular carcinoma
Administer the following vaccines: - Hepatitis A and B vaccine if patient is not immune - Pneumococcal vaccine if patient has not already been vaccinated - Annual influenza vaccine if patient is aged ≥50 years or has other indications for vaccination	**Determine with patient if the patient is a candidate for therapy:** - If patient is a potential candidate, check a baseline quantitative HCV RNA - Refer to a specialist for further management gastroenterology/ hepatology or infectious diseases)

Screening for Hepatocellular Carcinoma (HCC)

There is a high incidence of HCC in HCV-infected patients with cirrhosis, and appropriate screening strategies are not yet clear. As of February 2005, the National Cancer Institute noted that there was still "inadequate evidence to suggest that screening would restult in a decrease in mortality from hepatocellular cancer." At present, depite the lack of firm evidence for efficacy of surveillance, it remains standard practice to screen for HCC.

Pharmacologic Therapy

The ultimate goal of treatment is sustained virologic response (SVR), which is associated with a decreased risk for liver-related death and overall mortality (Table 8).

The treatment of choice for HCV-infected patients is the combination of pegylated interferon and ribavirin. Pegylated interferon is administered subcutaneously; ribavirin is taken orally. The best predictors of SVR are infection with HCV genotype 2 or 3, and a low pretreatment viral load.

Adverse events associated with interferon include flu-like symptoms early in treatment, depression, fatigue, concentration and memory disturbances, neutropenia, thrombocytopenia, hypo- and hyperthyroidism, retinal disturbance, interstitial pulmonary fibrosis, and suicidal ideation. Adverse effects are less frequent with pegylated interferon. Adverse events associated with ribavirin include rash, pruritis, hemolytic anemia, gout, and birth defects.

TABLE 8: TREATMENT RESPONSE DEFINITIONS

TREATMENT RESPONSE	DEFINITION
Sustained virologic response	- Absence of HCV RNA in the serum at the end of treatment and 6 months later - Infection is considered eradicated
Relapse	HCV RNA becomes undetectable on treatment, but is detected again when therapy is discontinued
Non-responders	Persons in whom HCV RNA levels remain stable on treatment
Partial responders	Persons in whom HCV RNA levels decline, but never become undetectable

Contraindications to Therapy

Because the available medications can cause serious adverse events, the decision to pursue pharmacologic therapy should be discussed in detail with the patient. A patient should not be considered a treatment candidate if he or she cannot keep scheduled appointments reliably. There are several conditions in which pharmacologic therapy is contraindicated, thus patients with these conditions should generally not be referred to a specialist for pharmacologic therapy (Table 5).

SPECIAL POPULATIONS

Pregnant Patients

The use of an interferon-based medication or ribavirin is contraindicated during pregnancy. Mother-to-infant transmission of HCV occurs only when the virus is detectable in the blood; the transmission rate is between 4% and 7%, increasing 4- to 5-fold with HIV co-infection.

Infants born to HCV-infected mothers should be tested for HCV infection. An infant may have maternal anti-HCV until 18 months of age. The Centers for Disease Control and Prevention recommends not testing for anti-HCV until a child is 19 months old, or a PCR may be done instead.

TABLE 9: ILLICIT DRUG USERS: ADVICE ABOUT HCV TRANSMISSION AND PREVENTION

Do not inject street drugs. If you do inject street drugs, enroll in a treatment program to stop.

If you cannot stop injecting drugs:

-- Never share your drug equipment (needles, syringes, water, cotton, cooker, ties, etc.)

-- Use sterile syringes and drug equipment every time you inject drugs.

-- Don't split drugs with a used syringe. If that is not possible, split drugs while they are still in powdered form.

-- Wash your hands and the injection site before and after shooting up.

-- Don't share straws if you snort drugs. Blood on the straw may spread the virus.

-- Get tested and vaccinated against hepatitis A and B.

-- Get tested for HIV.

There is not enough evidence to recommend that HCV-infected mothers avoid breast feeding. Mothers should, however, consider abstaining from breast feeding if nipples are cracked or bleeding.

Injection Drug Users

In the United States, HCV prevalence among persons who have ever used injection drugs is estimated at 57%. Sharing needles is the riskiest behavior, and a large percentage of injection drug users share needles. Although providers are often reluctant to treat active injection drug users, they should not reject patients for treatment on this basis alone, and should instead consider these patients on an individual basis. Interferon appears not to significantly change the pharmacokinetics of methadone. Active injection drug use does not appear to affect patient adherence, management regimen, or SVR. Providers should present HCV risk-reduction counseling regardless of the decision to treat (Table 9). Prior HCV infection, whether it has resolved spontaneously or via antiviral therapy, does not confer immunity. Thus, even if SVR has been achieved, there is a risk of reinfection.

Psychiatric disorders are common among patients with HCV who are active drug users. Interferon-based therapy in HCV-infected patients often causes depressive symptoms and has the potential to exacerbate a pre-existing psychiatric disorder. An increase in depressive symptoms may be associated with reduced viral clearance. Major depression should be treated; patients may be treatment candidates when their depression is controlled.

REFERENCES

American Liver Foundation
www.liverfoundation.org
(212) 668-1000
(800) 676-9840

Centers for Disease Control and Prevention (CDC)
www.cdc.gov/hepatitis

Harm Reduction Coalition
www.harmreduction.org;
NYC office: (212) 213-6376

Immunization Action Coalition
www.immunize.org
www.hepprograms.org

HCV Advocate
Hepatitis C Support Project
www.hcvadvocate.org

New Jersey Department of Health and Senior Services
www.state.nj.us/health/cd
(609) 588-7500

NJ Division of Addiction Svcs.
www.state.nj.us/humanservices/das/getting_help.htm

This module is based on a NYC Department of Health and Mental Hygiene (NYCDOHMH) Hepatitis C document and NJDHSS thanks NYCDOHMH for their assistance.