Hepatitis C: Diagnosis and Treatment

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Hepatitis C, a common chronic bloodborne infection, is found in approximately 2 percent of adults in the United States. Chronic infection is associated with serious morbidity and mortality (e.g., cirrhosis, hepatocellular carcinoma). Testing for hepatitis C is recommended for at-risk populations, and confirmatory testing includes quantification of virus by polymerase chain reaction. The U.S. Preventive Services Task Force recommends against routine screening for hepatitis C virus infection in asymptomatic adults who are not at increased risk of infection (general population). It found insufficient evidence to recommend for or against routine screening in adults at high risk of infection. Current therapy for chronic hepatitis C virus includes pegylated interferon and ribavirin. Therapy is based on factors that predict sustained virologic response, and the goal of therapy is to slow or halt progression of fibrosis and prevent the development of cirrhosis. In the future, multidrug regimens in combination with current therapies may be developed. Patients with chronic hepatitis C virus infection should be advised to abstain from alcohol use. Currently, there is no vaccine available to prevent hepatitis C virus infection; however, persons infected with hepatitis C virus should be vaccinated for hepatitis A and B. The American Association for the Study of Liver Diseases recommends ultrasound surveillance for hepatocellular carcinoma in persons with chronic hepatitis C virus infection and cirrhosis. (*Am Fam Physician*. 2010;81(11):1351-1357. Copyright © 2010 American Academy of Family Physicians.)

▶ **Patient information:** A handout on hepatitis C, written by the authors of this article, is provided on page 1359.

▶ See related article on hepatitis B in the April 15, 2010 issue of *AFP*.

EB CME

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An estimated 170 million persons, or 3 percent of the world's population, are chronically infected with the hepatitis C virus (HCV).[1] In the United States, the prevalence of hepatitis C antibody is 2 percent in adults 20 years and older, but the prevalence is higher in groups at increased risk (e.g., 8 to 9 percent in persons undergoing hemodialysis).[2,3] HCV, a single-stranded RNA virus, is transmitted through percutaneous exposure to infected blood.[4] HCV is categorized into nine genetically distinct genotypes.[5] In the United States, 72 percent of patients with HCV infection have genotype 1; 16 to 19 percent have genotype 2; 8 to 10 percent have genotype 3; and 1 to 2 percent have other genotypes.[6] This article focuses on chronic HCV infection in adults and excludes special groups, such as children, pregnant women, transplant recipients, and persons coinfected with hepatitis B virus (HBV) or human immunodeficiency virus (HIV).

Pathophysiology

The most common sources of HCV transmission are exposure to blood products before HCV testing procedures were routine; sharing of contaminated needles among injection drug users; and reuse of incompletely sterilized needles, syringes, or other medical equipment.[1,4,7] Risk factors for exposure to HCV are shown in *Table 1*.[8] Blood transfusions in the United States after 1992 have a very low risk of transmitting HCV (three per 10,000 units transfused).[9]

Screening and Prevention

The U.S. Preventive Services Task Force recommends against routine screening for HCV infection in asymptomatic adults who are not at increased risk of infection (general population). It found insufficient evidence to recommend for or against routine screening for HCV infection in adults at high risk of infection because no studies have proven that testing leads to a reduction in HCV-related morbidity and mortality.[2,10] A cohort study of 25,701 patients found that targeted screening leads to early identification of persons at increased risk of complications from HCV and those who may benefit from antiviral therapy (number needed to screen = 451).[11]

There is no vaccine available to prevent HCV infection. Patients with HCV infection should be considered for hepatitis A and B vaccination because of the increased risk of morbidity and mortality with coinfection.[4,12] HCV is not efficiently transmitted, and the average rate of seroconversion after

an occupational exposure to HCV-positive blood through accidental needlestick is 1.8 percent.[13] Persons should be tested for HCV following exposure through an accidental needlestick. Although there is no evidence to support the use of immune globulin therapy after an accidental needlestick,[13] a small case series of 44 patients suggests that treatment of persons with acute HCV infection may prevent progression to chronic HCV infection.[14]

Injection drug users should avoid needle sharing because it is the strongest independent risk factor for HCV infection.[2] An association between HCV infection and high-risk sexual behavior may be because of a high rate of sexual transmission or because high-risk sexual behaviors are a marker for unacknowledged drug use.[2] Persons at risk should use latex condoms with sexual activity.[12]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Persons who are not at increased risk (general population) should not be screened for HCV infection.	A	2, 10
Persons with HCV infection should be vaccinated for hepatitis A and B.	C	4
Persons with chronic HCV infection should abstain from alcohol consumption.	C	15-17
Hepatotoxic drugs should be avoided in persons with chronic HCV infection and cirrhosis.	C	3
Surveillance for hepatocellular carcinoma should be considered in persons with chronic HCV infection and cirrhosis.	C	18, 21
The standard therapy for chronic HCV infection is pegylated interferon and ribavirin (Rebetol).	C*	37, 38

HCV = hepatitis C virus.

**—Recommendation for treatment is "C" because the outcome is a surrogate marker (sustained virologic response) rather than mortality.*

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Diagnosis and Complications

Most patients (60 to 70 percent) with HCV infection are asymptomatic; when symptoms do occur, they are nonspecific and include fatigue, nausea, anorexia, myalgias, arthralgias, weakness, and weight loss.[1,7,12] Abnormal laboratory findings or signs of cirrhosis should prompt HCV antibody testing, followed by confirmatory tests.[2]

Chronic HCV infection leads to cirrhosis in about 10 to 20 percent of patients, increasing the risk of complications of chronic liver disease, including portal hypertension, ascites, hemorrhage, and hepatocellular carcinoma.[1,3] Factors associated with disease progression to cirrhosis include male sex, developing HCV infection when older than 40 years, HIV or HBV coinfection, immunosuppression, and daily alcohol consumption of at least 50 g (approximately three drinks per day).[15,16] Alcohol consumption and HCV act synergistically to promote the progression of liver damage. Persons with HCV infection who drink alcohol on a regular basis have a higher rate of fibrosis and cirrhosis.[16,17] The American Association for the Study of Liver Diseases (AASLD) recommends that persons with chronic HCV infection abstain from alcohol consumption.[15] Hepatotoxic drugs should be avoided in persons with chronic HCV infection and cirrhosis.[3]

Persons with HCV infection and cirrhosis have a 20-fold increased risk of hepatocellular carcinoma compared with persons without HCV infection.[18] Although uncommon in the United States (incidence of 8,500 to 11,500 cases per year), the incidence has increased approximately 70 percent in the past 30 years, and the prognosis is poor, with a median survival of eight months.[19,20] A recent meta-analysis found that ultrasound surveillance of persons at increased risk of hepatocellular carcinoma had a pooled sensitivity of 94 percent and specificity of 94 percent (positive likelihood ratio = 15.7; negative likelihood ratio = 0.1).[21] However, ultrasonography was less effective for detecting early hepatocellular carcinoma, with a sensitivity of only 63 percent.[21] The AASLD recommends surveillance for

Table 1. Risk Factors for Exposure to Hepatitis C Virus

Risk factor	*Odds ratio*
Intravenous drug use	36
Sex with intravenous drug user	17
Hemodialysis	8.3
Male sex	3.1
Blood transfusion	2.3
Sex with multiple partners	2.2
Surgery	1.0
White or Hispanic race	0.9
Age 40 to 60 years	0.8
Needlestick injury	0.7
Health care occupation	0.3
Vaccinated for hepatitis B	0.3

Information from reference 8.

Table 2. Diagnostic Tests and Test Results in Suspected HCV Infection

Initial anti-HCV tests	*Confirmatory HCV tests*		
*Enzyme-linked immunosorbent assay**	*Recombinant immunoblot assay*	*HCV RNA polymerase chain reaction*	*Test interpretation*
Negative	—	—	No infection or very early infection (repeat polymerase chain reaction if clinical suspicion of acute HCV infection)
Positive	Positive	Positive	Current infection
Positive	Negative	Negative	False-positive antigen test
Positive	Positive	Negative	Past infection with HCV

HCV = hepatitis C virus.

**—Including enzyme immunoassay or enhanced chemiluminescence immunoassay.*

Information from references 15 and 23.

hepatocellular carcinoma in persons with chronic HCV infection and cirrhosis based largely on a randomized study involving 18,816 patients with chronic HBV infection, which showed a 37 percent mortality reduction at one year favoring surveillance versus no surveillance.[18,22] However, there are no studies showing that ultrasound surveillance improves morbidity or mortality from hepatocellular carcinoma.

Diagnostic Testing

Diagnostic tests used for the detection of HCV infection include the HCV antibody enzyme immunoassay, recombinant immunoblot assay, and quantitative HCV RNA polymerase chain reaction (PCR). *Table 2* lists common diagnostic tests,[15,23] and *Table 3* lists the diagnostic precision of various tests.[2,24-27]

The most widely used initial assay for detecting HCV antibodies is the enzyme immunoassay. A positive enzyme immunoassay should be followed by a confirmatory test. When used in low-risk groups, an enzyme immunoassay may yield false-positive results.[24] A saliva-based test for HCV antibody detection may soon be available.[25] Recombinant immunoblot assay, a confirmatory test for a positive enzyme immunoassay, detects antibodies to individual HCV antigens and has a greater specificity.[26] It is used in conjunction with viral load tests to distinguish between a resolved infection and a false-positive enzyme immunoassay.

Quantitative viral load tests measure the amount of virus in blood. Quantitative studies provide information on initial viral load, viral load reduction with therapy, and a sustained virologic response, defined as undetectable HCV by PCR six months after stopping therapy.[15] However, HCV RNA levels do not correlate directly with liver injury, duration of infection, or disease severity.

Treatment

The goal of therapy is to slow or halt progression of fibrosis and prevent the development of cirrhosis, thereby helping patients live longer, symptom-free lives.[28] Sustained virologic response is the surrogate marker used by most studies to evaluate the effectiveness of therapy and

Table 3. Diagnostic Precision of Laboratory Tests for HCV Infection

Test	*Sensitivity (%)*	*Specificity (%)*	*Positive likelihood ratio*	*Negative likelihood ratio*	*Positive predictive value* (%)*	*Negative predictive value* (%)*
Recombinant immunoblot assay†	79	80	3.95	0.26	7.5	99.5
Saliva-based anti-HCV	87	99	87	0.13	64	99.7
Anti-HCV‡	94 to 100	97 to 98	31 to 49	0.06 to 0.01	39 to 50.4	99.9 to 100
HCV RNA polymerase chain reaction§	96	99	96	0.04	66.2	99.9

HCV = hepatitis C virus.

**—Assume prevalence of 2 percent.*[2]

†—*Third-generation.*

‡—*Third-generation enzyme-linked immunosorbent assay.*

§—*Specificity based on COBAS Amplicor test.*

Information from references 2, and 24 through 27.

Table 4. Virologic Response to Treatment for HCV Infection and Recommendations to Discontinue Therapy

Interpretation of quantitative HCV RNA	*Virologic response*	*Decision to continue or discontinue treatment*
Undetectable virus at week 4 of treatment	Rapid virologic response (predictive of sustained virologic response)	Consider early discontinuation for genotype 1a or 1b at week 24 if viral load < 600,000 IU per mL and for genotype 2 or 3 at weeks 12 to 16 because these levels are highly predictive of sustained virologic response
More than 100-fold decrease in viral load at week 12 of treatment	Partial virologic response	Recheck viral load at week 24; if undetectable, continue treatment until week 48
		If detectable, consider prolonged treatment until week 72
Undetectable virus at week 12 of treatment	Complete virologic response	Continue treatment until week 48
Stable viral load or failure to achieve more than 100-fold decrease in viral load at week 12 of treatment	Nonresponse	Discontinue treatment
Undetectable viral load six months after ending treatment	Sustained virologic response	HCV infection eradicated

HCV = hepatitis C virus.

Information from references 15 and 31.

is associated with improved outcomes, such as low likelihood of viral relapse, reduced mortality, and reduced risk of cirrhosis and hepatocellular carcinoma.[29,30] *Table 4* lists virologic responses to treatment of HCV infection.[15,31] All persons with chronic HCV infection should be considered candidates for treatment; however, several factors influence the decision to proceed with therapy.[32] Nonmodifiable factors, such as the presence of genotype 1, a high viral load, obesity, black or Latino race, advanced age, and the degree of liver fibrosis, indicate a lower probability of response to therapy.[33,34] Treatment for HCV infection is widely accepted in persons at least 18 years of age who are willing to be treated and to conform to treatment requirements, with abnormal serum alanine transaminase (ALT) values, significant liver fibrosis or compensated cirrhosis, and normal renal function, and without anemia or neutropenia.[32]

A detailed history and examination should be performed to identify contraindications to therapy *(Table 5)*.[32] Before starting therapy, baseline blood work should be obtained, including a complete blood count, complete metabolic panel, and measurement of thyroid-stimulating hormone level, because interferon therapy is associated with leukopenia, thrombocytopenia, and autoimmune thyroiditis. Persons with chronic HCV infection and anemia, renal insufficiency, autoimmune hepatitis, decompensated cirrhosis, pregnancy, severe cardiopulmonary disease, uncontrolled major depression, or untreated hyperthyroidism are not good candidates for treatment.[32] Blood urea nitrogen and serum creatinine levels should be evaluated because ribavirin (Rebetol) is renally excreted and should be used with caution in patients with renal insufficiency.

Serum aspartate transaminase (AST) and ALT levels

Table 5. Contraindications to Treatment for Chronic HCV Infection

Absolute contraindications

Active autoimmune hepatitis or other condition known to be exacerbated by interferon and ribavirin (Rebetol)

Known hypersensitivity to drugs used to treat HCV infection

Pregnant or unwilling to comply with adequate contraception

Renal failure (contraindicated for ribavirin only)

Severe concurrent cardiopulmonary disease

Uncontrolled major depressive illness, psychosis, or bipolar disorder

Untreated hyperthyroidism

Relative contraindications

Decompensated cirrhosis:

- Albumin level less than 3.4 g per dL (34.00 g per L)
- Evidence of encephalopathy or ascites
- International Normalized Ratio greater than 1.5
- Platelet count less than 75 x 10^3 per mm^3 (75.00 × 10^9 per L)
- Total serum bilirubin level greater than 1.5 mg per dL (25.66 µmol per L)

Baseline hematologic and biochemical indices:

- Hemoglobin level less than 13 g per dL (130.00 g per L) for men and 12 g per dL (120.00 g per L) for women
- Neutrophil count less than 1,500 per mm^3 (1.50 × 10^9 per L)
- Serum creatinine level greater than 1.5 mg per dL (132.60 µmol per L)

HCV = hepatitis C virus.

Adapted with permission from Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. Hepatology. *2004;39(4):1155.*

Table 6. Recommended Treatment for Chronic Hepatitis C Virus Infection by the Most Common Genotypes in the United States

Genotype	*Injectable*	*Oral*	*Duration (weeks)*	*Rate of sustained virologic response (%)*
1a and 1b	Pegylated interferon alfa-2a (Pegasys), 180 mcg weekly *or* Pegylated interferon alfa-2b (Pegintron), 1.5 mcg per kg weekly	Weight 165 lb (75 kg) or less: ribavirin (Rebetol), 1,000 mg daily Weight greater than 165 lb: ribavirin, 1,200 mg daily	48	45 to 50
2 and 3	Same as above	Ribavirin, 800 mg daily	24	70 to 80
4	Same as above	Weight 165 lb or less: ribavirin, 1,000 mg daily Weight greater than 165 lb: ribavirin, 1,200 mg daily	48	70

NOTE: *The contents of this table are based on scientific evaluation and package inserts with no commercial interest. These are commonly used dosages and durations, and may not reflect package insert information.*

Information from references 32 and 41.

may be normal in 10 to 40 percent of patients with chronic HCV infection.[12] Although there is a poor correlation between serum ALT level and severity of liver disease, monthly monitoring of AST and ALT levels is recommended during treatment for HCV infection and at three and six months following treatment.[12] A scoring system using platelet count and AST and albumin levels predicts severe fibrosis with 99 percent specificity and 94 percent positive predictive value.[35] Genotype identification assists in predicting response to treatment because persons with genotype 1 have lower rates of response to therapy than patients with genotypes 2 and 3.[36] Liver biopsy to assess disease severity may be considered when deciding whether to initiate treatment in patients with chronic HCV infection and persistently normal transaminase levels or with relative contraindications to therapy, or for prognostic purposes (e.g., in patients with genotype 1).[12,26]

Treatment Options

Standard therapy for the treatment of chronic HCV infection is pegylated interferon and ribavirin.[37,38] Oral ribavirin monotherapy is not effective for inducing sustained virologic response (relative risk = 1.01; 95% confidence interval, 0.96 to 1.07).[39] There are two formulations of pegylated interferon that are approved for HCV therapy: pegylated interferon alfa-2a (Pegasys) and pegylated interferon alfa-2b (Pegintron). Sustained virologic response rates for pegylated interferon monotherapy and pegylated interferon plus ribavirin are 25 to 39 percent and 54 to 60 percent, respectively (number needed to treat = 1.7 to 1.9 for sustained virologic response for pegylated interferon plus ribavirin, compared with placebo).[2] A recent randomized controlled trial compared pegylated interferon alfa-2b plus ribavirin with pegylated interferon alfa-2a plus ribavirin and found no statistical difference for sustained virologic response.[40]

The duration of therapy is determined by HCV genotype and virologic response to therapy. In general, patients with genotypes 1 and 4 are treated for 48 weeks, and those with genotypes 2 and 3 are treated for 24 weeks.[15] *Table 6* lists the recommended drugs and duration of treatment for HCV infection based on genotype.[32,41] The quantitative HCV RNA level is used to assess response to therapy and as a guide to discontinue treatment. A negative viral load test after four weeks of therapy is predictive of sustained virologic response.[15] In contrast, failure to achieve a 100-fold reduction in viral load by week 12 of therapy has a strong negative predictive value for sustained virologic response and suggests that treatment is likely ineffective and should be stopped. *Table 7* lists factors that predict sustained virologic response.[15,33]

Table 7. Predictors of Sustained Virologic Response to Treatment for Chronic HCV Infection

Absence of cirrhosis
Age 40 years or younger
Alanine transaminase level greater than three times the upper limit of normal
Completed 48 weeks of therapy for genotypes 1 and 4, or completed 24 weeks of therapy for genotypes 2 and 3
Compliance with treatment
Female sex
Genotypes 2 or 3
Lower body weight (body mass index less than 25 kg per m^2)
Low HCV RNA level (< 500,000 IU per mL)
White race

HCV = hepatitis C virus.

Information from references 15 and 33.

Table 8. Adverse Effects of Pegylated Interferon and Ribavirin (Rebetol) for the Treatment of Hepatitis C Virus Infection

Frequency (%)	*Adverse effects*
< 1	**Cardiovascular**
	Angina pectoris; heart failure; myocardial infarction
	Neurologic
	Coma; confusion; neuropathy; retinal hemorrhage; seizures; stroke; tinnitus; vision loss
	Psychiatric
	Acute psychosis; attempted suicide; hearing loss; panic attacks; suicidal ideation
	Other
	Autoimmune diseases; renal, cardiac, or pulmonary failure; worsening of hepatitis
1 to 5	**Psychiatric**
	Severe anxiety and depression; substance abuse or relapse of alcohol abuse
	Other
	Induction of autoantibodies; severe bacterial infection
> 5	**Constitutional symptoms**
	Arthralgias; fatigue; fever; malaise; myalgias; nasal stuffiness
	Dermatologic
	Hair loss; itching; photosensitivity; rash
	Gastrointestinal
	Abdominal discomfort; diarrhea; nausea; poor appetite
	Hematologic
	Anemia; hemolysis; neutropenia; thrombocytopenia
	Neurologic and psychiatric
	Anger; anxiety; depression; difficulty concentrating and sleeping; emotional lability; headache; irritability; memory loss
	Other
	Local erythema, pain, or abscess at injection site

Information from reference 32.

ADVERSE EFFECTS OF TREATMENT

Adherence to treatment remains a major factor influencing the rates of sustained virologic response.[33,42] Discontinuation of therapy because of adverse events is common and has been reported in up to one third of patients. Approximately 50 to 60 percent of patients may exhibit self-limited influenza-like symptoms with interferon-based therapy.[2] Effective management of treatment-related adverse events is essential to improve adherence to treatment; therefore, patients should be monitored closely for hematologic, renal, and thyroid abnormalities. Approximately 30 percent of patients undergoing treatment for HCV infection experience depression, emotional lability, or anger, but treatment is rarely associated with suicidal ideation or hallucinations.[43] Treatment for HCV infection is contraindicated in persons with uncontrolled major depression.[32] A recent randomized trial found that the overall adverse effects of pegylated interferon alfa-2b plus ribavirin (8.6 percent) and pegylated interferon alfa-2a plus ribavirin (11.7 percent) were similar.[40] Adverse effects of pegylated interferon and ribavirin for the treatment of HCV infection are listed in *Table 8*.[32]

NEWER THERAPIES

Other interferons (consensus interferon and albinterferon alfa-2b) and ribavirin alternatives (taribavirin) are being developed to improve the effectiveness, safety, and tolerability of therapy for chronic HCV infection.[44] New protease inhibitors (telaprevir and boceprevir) are actively being investigated in phase 3 clinical trials.[40,45] In the future, multidrug regimens will probably be used in combination with interferon and ribavirin.

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Author disclosure: Nothing to disclose.

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