

The Diagnosis and Management of Hepatitis C: The Role of the Physician Assistant

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Citation

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Abstract

Hepatitis C will pose a serious challenge to the health care system during the next 2 decades. Physician assistants can play an important role in the screening, diagnosis, and management of hepatitis C infection, and in educating patients about this disease. Screening for risk factors for hepatitis C virus (HCV) can be used to identify most infected individuals, who can then be tested for the presence of anti-HCV antibodies and HCV RNA. Hepatitis C can be treated with a combination of pegylated interferon plus ribavirin, and the virus can be cleared in a significant percentage of infected individuals.

HEPATITIS C: SCOPE OF THE PROBLEM

The United States faces a major public health challenge over the next 2 decades from the largely silent but widespread infection of adults by HCV. This is now the most common blood-borne infection in the United States. ¹ About 2% of adults in this country are infected, but only a small fraction of these individuals have been identified and are aware of their positive viral status. ^{1,23} The Centers for Disease Control and Prevention (CDC) estimated that there were approximately 30,000 new cases of HCV infection in 2003. ⁴ These estimates are probably conservative, because the National Health and Nutrition Examination Survey (NHANES) data on which they were based excluded people who were incarcerated or homeless, individuals known to have high rates of HCV infection. ^{3,4}

Chronic HCV infection is defined as the persistence of HCV RNA in the blood for at least 6 months. ² Chronic HCV is frequently asymptomatic in its early stages, and years or decades may pass before affected individuals seek treatment. ⁵ Even symptomatic individuals may complain of only vague feelings of tiredness or malaise, leading to delays in diagnosis if HCV is not suspected. ⁵ HCV-infected patients may progress to very grave illnesses, chief among them being the occurrence of silent but progressive fibrotic liver disease. ⁶ The rate of progression to cirrhosis varies widely in infected patients, but it is currently estimated that up to 20% of patients infected with HCV will develop cirrhosis over a 20- to 25-year period. ⁷ Many of these patients may

progress to end-stage liver disease and death unless a transplant is performed, and HCV infection has now become the most common reason for liver transplantation in the US. ^{7,8} Once an HCV-infected individual develops cirrhosis, the risk of hepatocellular carcinoma is also present, contributing to mortality rates. ⁷ Because HCV is a systemic disease, infected patients can also develop serious extrahepatic complications of immunologic origin, including rheumatoid symptoms, kidney disease, and skin disorders. ²

If HCV-infected individuals are not identified and treated, deaths due to HCV infection are expected to increase 2- to 3-fold by 2010 to 2020, and annual deaths from HCV infection will exceed deaths from HIV/AIDS. ⁹ Physician assistants (PAs) can play important roles in identifying these individuals and helping to manage their disease, with the goal of lessening the overall health care burden and reducing the risks of mortality and morbidity from this deadly but still largely silent outbreak.

HEPATITIS C: A TREATABLE DISEASE

The current standard of care for HCV infection is combination therapy with pegylated interferon (IFN) alfa and ribavirin. ¹⁰ Interferons are naturally occurring proteins that have antiviral, immunomodulatory, and anti-inflammatory properties. ¹¹ Interferon alfa-2a and interferon alfa-2b have been shown to inhibit HCV replication and strengthen the host immune response to the virus. ¹¹ Pegylated interferons are interferons that have been conjugated to inert polyethylene glycol (PEG) moieties. ¹¹

Interferon alfa-2b is conjugated 1:1 to an unbranched, 12-kilodalton (kd) PEG moiety to form peginterferon alfa-2b, whereas interferon alfa-2a is conjugated 1:1 to a branched, 40-kd PEG moiety to form peginterferon alfa-2a.¹² Pegylation protects the molecules from enzymatic degradation and reduces their rate of renal elimination, thereby creating more desirable, longer-acting agents.¹¹ The combination of pegylated interferon plus ribavirin has been shown to be more effective than either pegylated interferon monotherapy or combination therapy with standard interferon plus ribavirin in inducing a sustained virologic response (SVR), defined as the complete absence of detectable HCV RNA in serum 6 months after the end of treatment.^{13,14,15}

The virus that causes hepatitis C is an RNA virus, and 6 genotypes of this virus have been identified to date.² Genotypes 1, 2, and 3 are the most common types found in the US population.³ The effectiveness of combination therapy varies with the viral genotype, with the criterion of effectiveness being SVR.² Up to 80% of patients infected with HCV genotypes 2 and 3 achieve SVR with combination treatment, compared with about 50% of patients infected with HCV genotype 1.⁷ Although this is a good success rate, especially for patients infected with HCV genotypes 2 and 3, only about 30% of individuals identified as having chronic HCV infection and considered good candidates for antiviral therapy currently receive treatment.¹⁶ In addition, a significant proportion of patients who achieve SVR—as high as 50%—also experience an improvement in liver histology.^{17,18}

17,18

THE ROLE OF THE PA IN THE DIAGNOSIS AND TREATMENT OF HCV INFECTION

Many of the skills associated with the PA as a physician extender are particularly important in the identification of patients who have acute or chronic HCV infection.¹⁹ PAs also can provide extensive help to patients in the pharmacologic treatment and daily management of the disease.¹⁹ These skills include:

1. Screening patients for the presence of occult diseases. PAs can order the appropriate tests to identify HCV infection and rule out other causes of hepatic disease
2. Taking complete medical histories. PAs can assess pre-existing medical conditions and determine the presence of key risk factors for HCV infection

3. Performing physical examinations. PAs can determine whether there are signs of cirrhosis or extrahepatic symptoms of HCV infection
4. Providing patient education on HCV infection and its treatment. PAs can provide appropriate information about the virus, the disease it causes, and its modes of transmission, as well as information about combination therapy regimens, in ways readily understood by patients
5. Providing referrals to specialists, including gastroenterologists, hepatologists, dermatologists, infectious disease specialists, psychiatrists/counselors, and nutritionists
6. Working with other health care professionals to help patients manage the side effects associated with combination therapy. Some of these side effects are particularly intense during the initial months of therapy, and PAs can help patients prepare for these side effects and manage them so that adherence to treatment is maintained

Although the number of PAs entering the subspecialty of hepatology is increasing, PAs who work in family practice or internal medicine settings are in key positions to identify patients infected with HCV and to provide these patients with crucial information and support.¹⁹

SCREENING PATIENTS FOR HCV INFECTION IDENTIFYING RISK FACTORS WHILE TAKING A MEDICAL HISTORY

The process of taking a good medical history is particularly important in dealing with patients with undiagnosed HCV infection. The PA is trained in taking medical history and knows the importance of early detection of diseases in general, particularly when interventions can have an impact on disease progression and long-term outcome. In addition, the PA is knowledgeable about basic principles of secondary prevention of disease.

Currently, most public health authorities recommend HCV screening for high-risk groups, both to enable treatment of infected patients as early in the course of disease as possible and to prevent infected patients from infecting other individuals.²⁰ A number of risk factors have been identified (Table 1). Patients positive for 1 or more risk factors should be considered candidates for HCV testing. In more than 90% of cases of HCV infection, a risk factor can be identified

with careful questioning. 7 Some of the most significant risk factors are associated with exposure to infected blood, the primary route of HCV transmission. 2

1. Injection drug use. Individuals most affected by HCV infection are present and former injection drug users; estimates of the percentage of these individuals who are seropositive for HCV infection range from 60% to 80%. 8 Intranasal cocaine may also be a risk factor. 2
2. Blood transfusion. Between January 1988 and June 1992, an estimated 300,000 Americans received blood transfusions contaminated with HCV, although blood screening instituted since mid-1992 has reduced the risk to less than 1 in 100,000 units. 5 Blood-derived products manufactured prior to 1987, when viral inactivation practices were initiated, and HCV-contaminated immune globulin were also sources of infection. 7,20,21,22
3. Hemodialysis or multiple surgeries. These procedures are associated with risk of developing HCV infection through increased risk of contact with infected blood. 7,20
4. Sexual transmission is relatively infrequent because of the low levels of virus in semen, saliva, and vaginal secretions. The rate of sexual transmission of HCV is generally accepted to be low, with an overall risk of <5%, and studies of long-term monogamous couples suggest a low risk of transmission from an infected individual to his/her spouse or partner. 5,23
5. Maternal transmission may occur in about 5% of newborns of HCV-infected mothers. 5,24 Breastfeeding need not be restricted in infected mothers, since the transmission of virus through breast milk has not been demonstrated. 5,24
6. Needle-stick transmission among health care professionals is low, occurring in approximately 2% of cases. 5
7. Needle-involved procedures such as body piercing, tattooing, or acupuncture. 25,26,27,28 Individuals who underwent these procedures in licensed establishments, however, are at very low risk for HCV infection, and the CDC recommends they not be routinely tested. 7,8

8. HCV infection is more likely to be diagnosed in certain other subpopulations, including Vietnam-era military veterans and persons with other blood-borne viruses (hepatitis B and HIV) or sexually transmitted diseases. 29

Figure 1

Table 1: Risk Factors Suggesting the Need to Screen for HCV Infection. ,,

<ul style="list-style-type: none"> • Injection with illicit drugs, even once, whether recently or in the remote past • Transfusion with blood or blood products later found to test positive for the presence of HCV or from donors who later tested positive for HCV infection • Medical conditions that may increase exposure to HCV virus, such as chronic hemodialysis or hemophilia that required the use of clotting-factor concentrates before 1987 • Persistently abnormal serum aminotransferase activities • Recipients of blood transfusions or organ transplants prior to July 1992 • A needle-stick injury or mucosal/cutaneous exposure to blood positive for HCV • Children born to HCV-positive mothers • Current sexual partners of HCV-infected patients, although the risk of infection is low • Persons from areas of high prevalence of HCV infection • Persons with HIV infection

Adams PC et al. Screening in liver disease: report of an AASLD clinical workshop. *Hepatology* 2004;39:1204-1212 © 2005. Adapted with permission from John Wiley and Sons, Inc.

Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Recomm Rep* 1998;47(RR-19):1-39. Adapted with permission.

Many HCV-infected patients are likely to have multiple or overlapping risk factors, whereas some may not have any identifiable risk factors. Given time constraints, it is not feasible to screen all patients for HCV infection. Rather, a PA who identifies at least 1 risk factor from taking a routine medical history can follow up with a more specific assessment, including possible past and present symptoms of acute or chronic HCV infection. Chronic infection, especially in its early stages, is only infrequently associated with symptoms, although some patients complain of nonspecific symptoms such as fatigue. 31

DETECTING CERTAIN SIGNS OR SYMPTOMS DURING PHYSICAL EXAMINATION

During a physical examination, PAs may detect signs or symptoms that suggest infection with HCV. Among the symptoms associated with acute infection are malaise, weakness, anorexia, and jaundice, although these symptoms are uncommon. 2 In addition to malaise, other symptoms/signs of chronic infection can include hepatomegaly, anorexia, nausea, right upper-quadrant pain,

dark urine, and itching.^{31,32} Additional physical symptoms/signs of the cirrhosis that accompany later stages of HCV infection include portal hypertension, variceal bleeding, ascites, and jaundice. HCV is also associated with extrahepatic disorders of the kidney, joints, and skin, as well as vasculitis, and these types of disorders should raise suspicion for HCV infection.^{33,34,35} However, it is critical for the PA to remember that a patient who is infected with HCV, but has not yet developed cirrhosis, will frequently present with no signs of disease during a physical exam.

REVIEWING LABORATORY TESTS FOR RESULTS THAT SUGGEST INFECTION

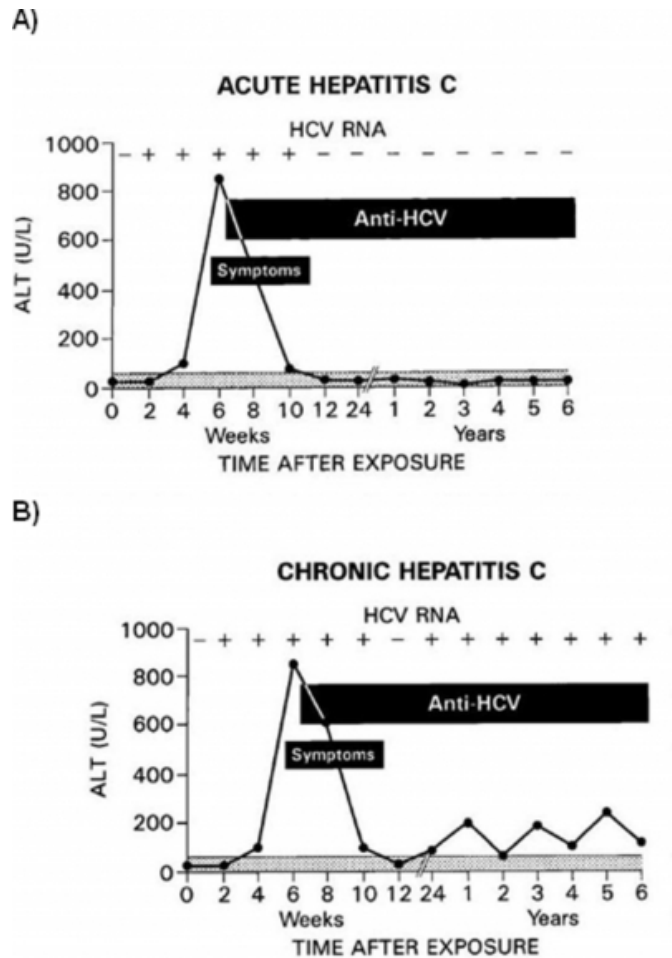
Elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity to 1.5- to 10-times the upper limit of normal are present in the majority of patients chronically infected with HCV and are associated with the presence of antibody to HCV.^{36,37} Moreover, elevated ALT is associated with chronic HCV infection may predict an increased risk of hepatocellular carcinoma.³⁸ Thus, elevated ALT should increase suspicion of HCV infection, and the American Association of Liver Disease has recommended that individuals with otherwise unexplained elevations of ALT or AST be tested for HCV infection.^{7,31} However, approximately one third of patients with chronic HCV infection will not have elevated aminotransferase activities, whereas others may have only intermittent elevations.³¹

ORDERING LABORATORY TESTS FOR DETECTION OF HCV OR ANTI-HCV ANTIBODIES

Acute and chronic hepatitis C differ in their serologic courses (Figure 1) and natural history (Figure 2).^{31,39} In a typical case of acute HCV infection followed by viral clearance, the patient will develop measurable levels of HCV RNA soon after exposure to the virus. As an effective immune response is raised and anti-HCV antibodies are produced, the level of HCV RNA becomes undetectable. These antibodies persist for years after the infection has resolved (Figure 1A). In a typical case of chronic HCV infection, the same initial serologic results are seen, but the HCV RNA levels persist in the serum because the active infection continues (Figure 1B).

Figure 2

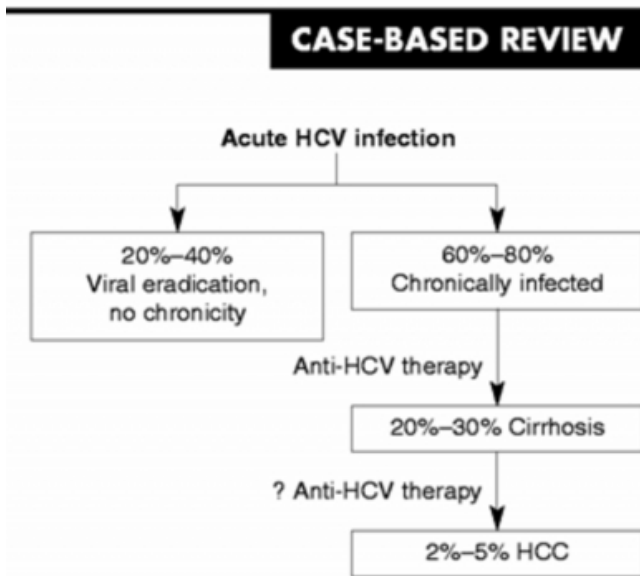
Figure 1: Serologic results in cases of acute hepatitis C that do not progress to chronic infection (A) and in cases of chronic hepatitis C (B).



Hoofnagle JH. Hepatitis C: the clinical spectrum of disease. *Hepatology* 1997;26(Suppl1):15S-20S © 2005. Printed with permission from John Wiley and Sons, Inc.

Figure 3

Figure 2: Natural history of HCV infection.



Reddy SI, Ukomado C. Hepatitis C: update on management of chronic infection. *J Clin Outcomes Manage* 2004;11:523-533. Printed with permission.

The tests most frequently used to screen for antibody to HCV are enzyme-immunoassays (EIA) (Table 2). These tests are reproducible and inexpensive, and are approved by the Food and Drug Administration (FDA) for the diagnosis of HCV infection. The current third-generation tests screen for antibodies directed against both viral-core proteins and nonstructural proteins. These tests have a high sensitivity and specificity for HCV infection in immunocompetent patients and are suitable for testing patients with liver disease. A negative result in immunocompetent patients can rule out infection, but false negative results may be obtained when testing patients on hemodialysis or those who have immune deficiencies. Conversely, testing patients with autoimmune disorders may yield false positive results for HCV antibody, and these patients require further testing for HCV RNA. Another method of assaying for HCV antibodies, called the recombinant immunoblot assay (RIBA), targets the same antigens as the EIA, and is helpful as a supplemental assay for those patients who test positive for antibodies by EIA but do not test positive for HCV RNA.

2

Figure 4

Table 2: Laboratory Tests Used in the Clinical Diagnosis of HCV Infection ,,,

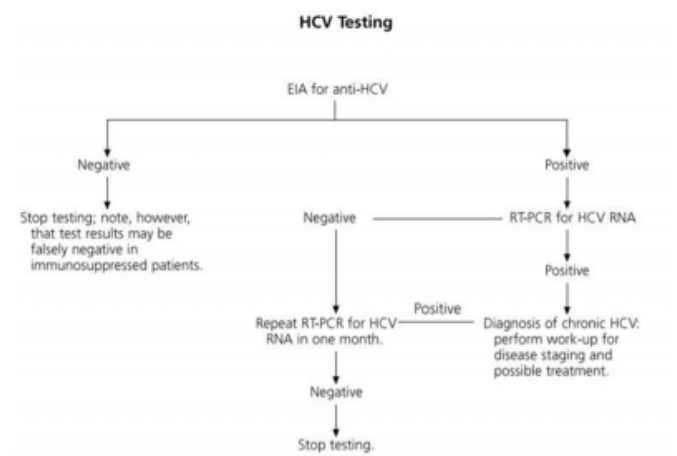
Test	Description
EIA (enzyme immunoassay)	Third generation test has a sensitivity of 98.8%-100% in immunocompetent patients Recommended screening test for HCV infection False-negative results more common in patients on hemodialysis and other immunocompromised groups, as well as individuals with mixed cryoglobulinemia
Qualitative HCV RNA	Reverse transcription polymerase chain reaction (RT-PCR) amplification or transcription-mediated amplification (TMA) of viral RNA genome Single positive result confirms HCV infection; single negative result may be due to low blood level of virus and does not confirm absence of infection More sensitive than quantitative test for HCV RNA
Quantitative HCV RNA	Target amplification or signal amplification method used in the quantification of HCV RNA blood levels Less sensitive than the qualitative test for HCV RNA

Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Recomm Rep* 1998;47(RR-19): 1-39. Adapted with permission.

Positive screening-test results for HCV antibody should be confirmed by a qualitative or quantitative assay for HCV RNA (Figure 3). A positive result is sufficient to confirm active HCV replication. A negative result, however, may indicate only that the viral load has dropped below the detection level of the assay, making it necessary to perform an additional HCV RNA test. If an individual is positive for HCV RNA, repeat testing can be used to determine whether an acute HCV infection has resolved without treatment. HCV RNA tests can be performed prior to referring an antibody-positive patient for further follow-up; these will speed up the evaluation and protect patients with false-positive antibody screening tests from needless referrals and unnecessary worry. Quantitative tests of HCV RNA can be used to measure baseline viral concentrations and to assay response to antiviral therapy.

Figure 5

Figure 3: Testing algorithm for HCV infection in asymptomatic patients.



Ward RP, Kugelmas M, Libsch KD. Management of

hepatitis C: evaluating suitability for drug therapy. *Am Fam Phys* 2004;69:E1429-E1438. Printed with permission.

The other type of viral testing that is typically ordered is genotyping of the HCV virus, because the length of treatment and probability of attaining SVR are dependent on genotype. The results provide valuable information to the health care provider and patient, and may stimulate helpful discussions of the risks/benefits of antiviral therapy. ⁷

Following a positive diagnosis of HCV infection, other laboratory tests are often performed to detect the presence of cirrhosis. These include additional tests of hepatic function, a complete blood count, and an International Normalized Ratio (INR; prothrombin time) test. ²

PATIENT EDUCATION AND HCV INFECTION

Patient education is an essential first step in encouraging patients to become active participants in their own care. ¹⁹ Patients need to know that chronic HCV and cirrhosis are long-term diseases that can be treated and managed. Although more than 50% of patients with hepatitis C are cleared of virus with treatment, fewer than 20% of HCV infected patients are aware that treatment exists, and even fewer are aware that SVR is possible with treatment. ⁴⁴ The PA should, therefore, emphasize the importance of maintaining good adherence to antiviral regimens being critical to disease management. ¹⁹

Patients also need information about other measures they can take to improve their well-being and slow disease progression (Table 3). ¹⁹ Abstinence from alcohol is an important step in preventing further liver damage. Alcohol also interferes with response to antiviral therapy, and complete abstinence from alcohol is recommended before and during treatment. ² Safe levels of alcohol consumption after treatment are unknown, and moderate levels may accelerate HCV disease in some patients. ² Weight loss and moderate exercise are also recommended. Hepatitis C patients should be vaccinated against hepatitis A virus, and those who are seronegative for hepatitis B virus but have risk factors for HBV infection should be vaccinated against hepatitis B. ² Support groups may be particularly beneficial in helping patients make these lifestyle changes. ⁴⁵

Figure 6

Table 3: Lifestyle Changes Recommended/Not Recommended to Prevent Transmission of HCV Infection to Others ,

Lifestyle changes recommended	Lifestyle changes not recommended
Avoid sharing toothbrushes, dental or shaving equipment	Those in monogamous sexual relationships do not need to use barrier precautions
Cover bleeding wounds to prevent blood from coming into contact with others. Women should avoid sex during menses or use barrier methods. Barrier methods should also be used if other STDs are present or if patient has multiple partners	Since the HCV virus is not believed to be transmitted by casual contact, normal household/work activities do not need to be curtailed
Stop using illicit drugs; those who continue injecting drugs should not reuse or share needles, syringes, cotton, or other paraphernalia. Needles and syringes should be disposed of safely	Breast-feeding is not discouraged in HCV-positive nursing mothers
Do not donate blood, body organs, other tissues or semen	

At the same time, it is important to reduce patients' fears of the stigmas connected with a diagnosis of HCV infection. While some HCV-positive individuals may worry that the American public thinks HCV is associated with drug addiction and other unhealthy lifestyles, only 30% of adults surveyed actually expressed this opinion. ⁴⁴ Moreover, nearly 90% of Americans believe that people like themselves can become infected with HCV. ⁴⁴

Patients should be counseled with specific information about how to reduce the risk of transmitting the disease to others. ¹⁹ A survey reported that 32% of US adults believed, incorrectly, that the disease is transmitted through fecal contamination of food or water, and only about 60% realize that HCV is spread through contact with infected blood. ⁴⁴ While all infected patients should be given this information, it is particularly important for injection-drug users, the leading source of HCV infections today. ⁷ Patients infected with HCV should be told not to share toothbrushes or other dental equipment or shaving gear, to cover bleeding wounds, and to avoid sharing any drug paraphernalia. ⁷ Risk of sexual transmission is low, so barrier precautions are not needed in monogamous relationships. ⁷ Patients should also be advised not to donate any blood, organs, tissues, or semen. ⁷

Although most primary care physicians and PAs do not discuss liver biopsies with patients immediately after diagnosis, these health care providers should be generally familiar with this procedure, which is usually performed by a specialist. This information will enable PCPs and PAs to answer questions their patients may raise during long-term management of their disease.

TREATMENT FOR HCV INFECTION

The 2002 National Institutes of Health (NIH) consensus document on the management of hepatitis C identified all

HCV-infected patients as potential candidates for treatment with pegylated interferon and ribavirin. ² Treatment is particularly recommended for patients at greater risk of developing cirrhosis. Absolute contraindications include specific allergies to these drugs, active injection drug use or heavy alcohol consumption, pregnancy, and refusal to use effective contraception, since ribavirin is highly teratogenic (Table 4). ⁴³ Relative contraindications include anemia, leukopenia, and thrombocytopenia; autoimmune diseases, with the exceptions of Crohn's disease and ulcerative colitis; coronary artery disease; and severe psychiatric disease, especially severe depression or a history of psychosis (Table 4). ⁴³

Figure 7

Table 4: Contraindications to Treatment of HCV Infection with Interferon Plus Ribavirin. ,

Absolute	Interferon	Ribavirin
	Psychosis	Pregnancy
	Severe depression	Inability to use reliable contraception
	Symptomatic heart disease	Severe heart disease
	Seizure disorder	Anemia
	Organ transplantation	Hemoglobinopathies
	Sarcoidosis	Renal failure
	Intravenous drug use or heavy alcohol use	Intravenous drug use or heavy alcohol use
	Decompensated cirrhosis	Decompensated cirrhosis
Relative	Autoimmune disease	Uncontrolled hypertension
	Uncontrolled diabetes	Coronary artery disease
	Anemia, leucopenia, or thrombocytopenia	Anemia, leucopenia, or thrombocytopenia

Ward RP, Kugelmas M, Libsch KD. Management of hepatitis C: evaluating suitability for drug therapy. *Am Fam Phys* 2004;69:E1429-E1438. Printed with permission.

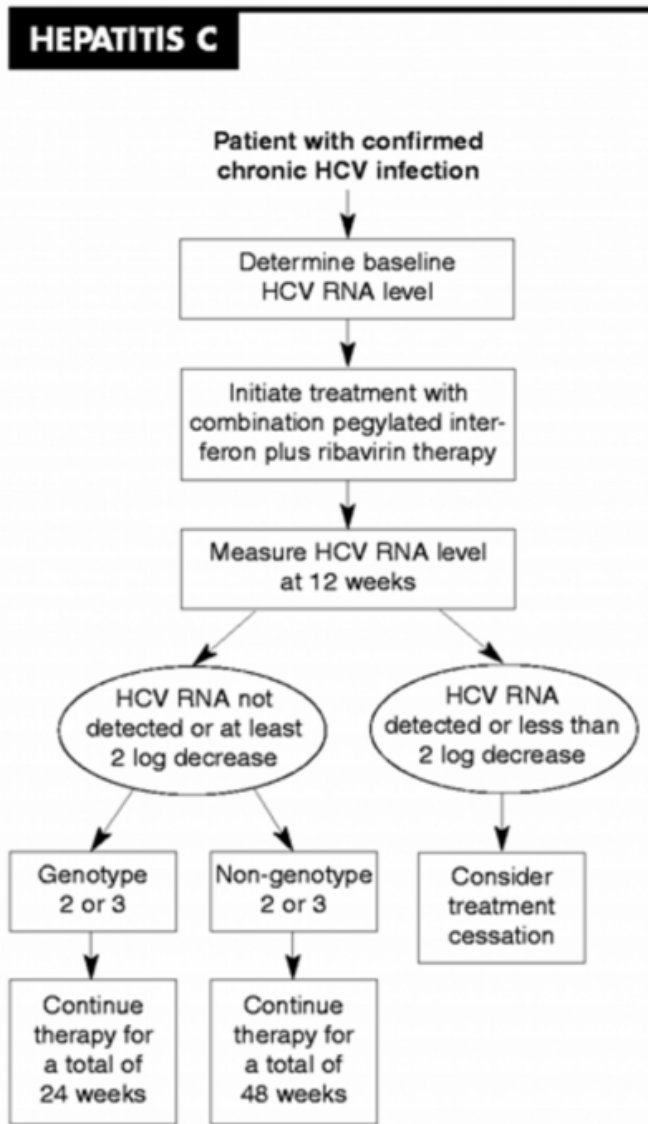
All patients diagnosed with HCV who are considered healthy enough for treatment should undergo evaluation by a physician experienced in the use of combination antiviral therapy, typically a gastroenterologist or hepatologist. ⁴⁷ The specialist may order a liver biopsy, HCV genotype testing, and quantitative HCV-RNA testing to help guide duration of antiviral therapy and to assess the likelihood of a response. Liver biopsy provides information about fibrosis and progression to cirrhosis that is not available through liver-enzyme testing. ² This gives HCV-infected patients information to help them decide whether to begin or postpone antiviral treatment. ² Patients with advanced liver disease should be referred to a center that can evaluate the need for, and perform, liver transplantation. ⁴⁷ Quantitative HCV RNA and HCV-genotype testing not only identifies patients most likely to respond to antiviral therapy but also helps determine the length and dose of treatment. Patients infected with genotypes 2 or 3 are typically treated for 24 weeks with a combination of peginterferon alfa-2a (180

µg/wk) or peginterferon alfa-2b (1.5 µg/kg/wk) and a reduced dose of ribavirin (800 mg/d), whereas patients with the more treatment-resistant genotype-1 virus are treated for 48 weeks with the same dose of pegylated interferon plus a higher dose of ribavirin, usually 1000 mg/d for patients weighing 75 kg or less and 1200 mg/d for patients weighing more than 75 kg. ² Quantitative HCV-RNA testing is performed in patients infected with HCV genotype 1 to provide an initial baseline value and to assess response during and after treatment.

Although most primary care PAs will not be directly involved in the administration of combination therapy, they may be involved in helping patients adhere to and manage treatment (Figure 4). Primary care PAs should, therefore, be aware of associated side effects that may have a negative impact on patient well-being and adherence to treatment. In some areas of the country, however, PAs specializing in gastroenterology or hepatology may be the health care providers most frequently involved in the long-term management of patients with HCV infection.

Figure 8

Figure 4: Treatment algorithm for chronic HCV infection.



Reddy SI, Ukomado C. Hepatitis C: update on management of chronic infection. *J Clin Outcomes Manage* 2004;11:523-533. Printed with permission.

The most common side effects of combination therapy are fatigue, influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms.⁴⁸ Other adverse events include cardiovascular, reproductive, respiratory, dermatologic, and gastrointestinal side effects.^{19,48} In clinical trials of pegylated interferon plus ribavirin, premature withdrawal from therapy due to adverse events occurred in 10% to 14% of participants, although most adverse events were managed by dose reductions.⁴⁸ Practical strategies for managing the most common of these diverse side effects have been detailed elsewhere.¹⁹

CONCLUSION

PAs are very familiar with the basic principles of disease prevention, diagnosis, and management, all of which are critical to the successful care of patients with HCV infection. PAs are likely to encounter many patients chronically infected with HCV and are in a position to utilize their skills to lessen the burden of this disease. These patients can be identified and treated in order to reverse, stop, or at least slow the progression of fibrotic liver disease and serious extrahepatic sequelae.

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