

## Approach to the Patient with Chronic Hepatitis C Virus Infection

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Chronic hepatitis C virus (HCV) infection is common and often asymptomatic. Antibodies against HCV are a highly sensitive marker of infection. Molecular testing for HCV is used to confirm a positive result on antibody testing and to provide prognostic information for treatment; however, quantitative HCV RNA does not correlate with disease severity or risk for progression. Chronic HCV infection is most frequently associated with remote or current intravenous drug use and blood transfusion before 1992, although as many as 20% of infected patients have no identifiable risk factor. In an estimated 15% to 20% of persons infected with HCV, the infection progresses to cirrhosis; alcohol intake is an important cofactor in this progression. Most specialists prefer to include an examination of liver histology in the management of patients with chronic HCV infection to aid prognostic and treat-

ment decisions. The current standard of pharmacologic treatment of chronic HCV is weekly subcutaneous peginterferon in combination with daily oral ribavirin, which results in sustained virologic response in approximately 55% of chronically infected patients. Side effects of interferon therapy include myalgias, fever, nausea, irritability, and depression. The cost-effectiveness of interferon therapy is similar to that of many commonly accepted medical interventions. The primary care physician serves a vital role in identifying patients with chronic HCV infection, educating patients about risk factors for transmission, advising patients about the avoidance of alcohol, and aiding patients in making treatment decisions.

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*A 50-year-old woman applies for life insurance. She is informed that the insurance company will not provide coverage because of the presence of hepatitis C virus (HCV) antibody. She feels perfectly well. Alarmed, she presents to your office with numerous questions about the accuracy of the test, confirmatory tests, her future insurability, threat to her future health, and the health risk to her family.*

### DO PATIENTS WITH CHRONIC HCV INFECTION TYPICALLY HAVE NO SYMPTOMS?

This patient's presentation is typical, since chronic HCV infection is often asymptomatic. Of persons with known HCV infection, only 25% to 30% seek medical attention for symptoms attributable to HCV infection; however, many of these symptoms, such as fatigue, are nonspecific (1). It is important to diagnose chronic HCV infection because the disease carries considerable morbidity and because therapy for the condition has improved dramatically in recent years. Chronic HCV infection is common in the United States, with an estimated prevalence of 1.8%.

### WHAT TESTS ARE USED TO SCREEN FOR HCV INFECTION, AND HOW ACCURATE ARE THEY?

Abnormal alanine aminotransferase (ALT) levels, if confirmed on repeated testing, should prompt a search for infection risk and a battery of serologic tests, including tests for hepatitis B virus (HBV) and enzyme immunoassay for HCV antibody (2). Because as many as 30% of

patients with replicative HCV infection have persistently normal ALT levels, a high index of suspicion is necessary to identify persons with chronic HCV infection (3). The U.S. Food and Drug Administration (FDA) requires testing of blood products for the presence of hepatitis B surface antigen and HIV but does not require testing for ALT or HCV (4). The American Association of Blood Banks does not recommend testing serum aminotransferase levels to screen allogeneic or apheresis donations; instead, it relies on HCV enzyme immunoassay (5). Life insurance companies often use serum aminotransferase levels for initial screening, followed by HCV enzyme immunoassay with confirmation by recombinant immunoblot assay. The sensitivity and specificity of currently used HCV enzyme immunoassays in high-prevalence populations range from 98% to 100% (6). These assays, available in kit form from several manufacturers, provide highly reproducible results (7). In low-prevalence populations, such as asymptomatic blood donors, 40% of anti-HCV-positive results on enzyme immunoassay represent false positives. Use of the recombinant immunoblot assay can be helpful in this situation (8). In clinical practice, confirmatory testing is always done, both to eliminate the possibility of a false-positive result on antibody testing and to provide prognostic information on antiviral therapy.

Tests for HCV RNA can involve target amplification (reverse transcriptase polymerase chain reaction [PCR]) or signal amplification (branched-chain DNA).

**Table 1. Serologic Tests for Hepatitis C Virus Infection\***

Test	Use	Comments	Approximate Cost, \$
Serum alanine aminotransferase	Screening	Widely available; reproducible results; nonspecific	35
HCV enzyme immunoassay	Screening	Reproducible; requires confirmation	100
Recombinant immunoblot assay	Confirmation	Most useful in low-risk blood donor situations	300
HCV RNA by PCR	Confirmation, quantitation of viremia	Sensitive and specific; technically demanding	250 to 700
HCV quantification by branched-chain DNA	Confirmation, quantitation of viremia	Reproducible; inaccurate with viral loads < 3200 copies/mL	250 to 350
HCV genotyping	Treatment prognosis	Can shorten course of antiviral therapy	350 to 750

\* HCV = hepatitis C virus; PCR = polymerase chain reaction.

For both types of assay, handling of specimens is important. Serum should be separated from whole blood within 4 hours of collection; to minimize freezing and thawing, the specimens must be stored at  $-70^{\circ}\text{C}$ . Polymerase chain reaction assays can detect fewer than 100 copies/mL of HCV viremia in serum or plasma; however, such assays have been hampered by a lack of standardization and reproducibility among laboratories. Automated kits are now used by many reference laboratories. Tests for HCV RNA that use PCR, with standardized units recorded in IU/mL, are expected to receive licensing from the FDA sometime this year. Branched-chain DNA can detect and quantitate HCV RNA levels as low as 3200 copies/mL, with lower cost and better reproducibility among laboratories. **Table 1** summarizes the most commonly used tests for diagnosis of HCV infection (9).

### SHOULD THE PHYSICIAN ORDER REPEATED HCV TESTING TO CONFIRM REPORTS OF INFECTION FROM SOURCES SUCH AS LIFE INSURANCE COMPANIES OR BLOOD DONATION CENTERS?

To screen for HCV infection, blood donation centers and life insurance companies now routinely use specific tests, such as HCV enzyme immunoassay with confirmation by recombinant immunoblot assay, instead of less specific measures, such as serum aminotransferase levels. The specificity and sensitivity of these tests are high enough to make confirmation unnecessary.

### ARE THERE LABORATORY TESTS OR IMAGING STUDIES THAT CLINICIANS SHOULD ROUTINELY INCLUDE IN THE EVALUATION OF ASYMPTOMATIC PATIENTS WHO ARE FOUND TO HAVE HCV INFECTION?

The quantification of HCV RNA has become an important part of the therapy for patients with chronic

HCV infection; however, it is important to note that there is no correlation between viral load and disease severity (10). The quantitative HCV PCR provides information on treatment success and duration but not about natural history of disease. Therefore, it is unnecessary to order serial measures of quantitative PCR in untreated patients. Several commercial assays, in addition to assays “home brewed” at individual hospital laboratories, are available for HCV quantification. The performance characteristics of these assays vary, and insurance considerations may limit their availability.

Hepatitis C virus has six major genotypes and more than 50 subtypes. This genetic heterogeneity may explain the resistance of HCV to therapy and vaccine development. Among U.S. patients with HCV infection, approximately 70% have genotype 1, 15% have genotype 2, and 10% have genotype 3 (11). Although HCV genotype does not correlate with disease severity, response rates to interferon-based regimens are substantially higher in patients infected with genotype 2 or 3 (12). Furthermore, patients infected with these more responsive genotypes can be treated with a shorter course of interferon-ribavirin therapy without substantial diminution of response rate (11). Therefore, it is recommended that genotype analysis be performed one time to provide information on expected response rates and duration of antiviral therapy. The HCV genotypes, which have about 65% genetic homology, are roughly geographically distributed. Types 1, 2, and 3 are most common in western Europe, North America, Australia, and the Far East (13). Type 4, which has been reported to respond poorly to interferon-based therapies, is found especially in the Middle East and in central and northern Africa (14). Genotype 5 is predominately found in South Africa, while genotype 6 is found almost exclusively in southeast Asia.

Patients with chronic HCV infection often have

normal results on ultrasonography of the right upper quadrant. Findings such as diffusely heterogeneous hepatic echotexture are nonspecific, representing inflammation, fatty infiltration, or fibrosis. Some investigators have found a correlation between enlarged perihepatic lymph nodes and hepatic histology (15). Ultrasonographic findings of abnormal hepatic contour, enlarged portal vein, or splenomegaly suggest cirrhosis; however, cirrhosis can often be diagnosed on the basis of careful physical examination. Currently, no evidence suggests the need for routine hepatic ultrasonography in patients with a diagnosis of chronic HCV infection. In patients with established cirrhosis, screening ultrasonography may allow early identification of hepatocellular carcinoma; however, the cost-effectiveness of this practice has been questioned (16, 17).

Chronic HBV infection, although less common than chronic HCV infection in the United States, remains an important cause of hepatic-related illness and must be considered in patients presenting with abnormal liver chemistries. Therefore, many patients with HCV infection have already been screened for hepatitis B surface antibody and hepatitis B surface antigen during serologic evaluation. Because the modes of transmission for HBV and HCV infection overlap considerably, patients with a diagnosis of HCV should be tested for the presence of chronic HBV infection. The mode of transmission of hepatitis A virus (HAV)—the fecal–oral route—differs substantially from that of HCV, and the prevalence of exposure to HAV has not been shown to be increased in patients with chronic HCV infection. However, vaccination strategies may require serologic measurement of patients' previous exposure to HAV.

Early reports of an overlap syndrome between autoimmune hepatitis and chronic HCV infection were confounded by the relatively high false-positive rate produced by the first-generation anti-HCV enzyme immunoassays (18). Nonetheless, patients with chronic HCV infection have been shown to manifest a higher-than-expected rate of autoantibodies in the serum (19). Because of numerous case reports of interferon-induced autoimmune disease, many investigators recommend checking for the presence of antinuclear antibody before initiating antiviral therapy. Although it is clear that the presence of an antinuclear antibody does not adversely affect the outcome of interferon therapy, such patients should be carefully monitored while receiving interferon for the development of autoimmune diseases, such as thyroiditis, rheumatoid arthritis, psoriasis, and systemic lupus erythematosus (20). Because interferon-induced thyroid disease is among the most common adverse events associated with interferon therapy, thyroid-stimulating hormone levels should be checked before therapy is initiated.

*Because the patient has abnormal levels of serum aminotransferases (two times the upper limit of normal) and a potential risk factor for infection, HCV RNA by PCR is used to confirm the diagnosis. The result is positive. The patient asks her physician how she became infected.*

## WHAT ARE THE RISK FACTORS FOR HCV INFECTION?

Chronic HCV infection is most frequently associated with remote or current intravenous drug use and blood transfusion before 1992. Other reported risks include drug inhalation, multiple sexual partners, body piercing, tattooing, needlestick injuries, immunoglobulin injection, hemo-

**Table 2. Risk Factors for Hepatitis C Virus Infection\***

Risk Factor	Comment	References
Transfusion of blood products	With modern screening, risk for HCV transmission is estimated at 0.01% to 0.001% per unit transfused	24–31
Intravenous drug use	Current or remote intravenous drug use accounts for 50% of new cases of HCV; 50% to 60% infected with HCV within 3 months of initiation of injection behavior	32, 33
Intranasal cocaine	Risk factor suggested by epidemiologic evidence	34–36
Tattooing	Remains controversial as a risk factor	37–39
Health care workers	Risk for HCV infection is fourfold that of blood donors; for needlestick injury, seroconversion rate is approximately 2%	40–45
Hemodialysis	U.S. patients receiving hemodialysis have 10% to 20% prevalence of chronic HCV infection	46–48
Sexual transmission	Estimated risk is 1% to 3% over lifetime of a monogamous relationship; barrier methods deemed unnecessary in monogamous couples	49
Vertical transmission	Estimated risk is approximately 5% per exposure; testing of infants not recommended before 1 year of age; breast feeding considered low risk	50–52

\* HCV = hepatitis C virus.

dialysis, and religious scarification (21–23). **Table 2** summarizes the most important risk factors associated with the transmission of HCV infection.

*The patient denies any history of blood transfusion or intravenous drug use but reports that she used intranasal cocaine several times in college. She remains concerned because she has read print and Internet articles that have reported an association between HCV infection and intravenous drug use and have painted a grim picture of disease outcome. The patient also has read that HCV infection is the leading cause of liver transplantation in the United States. She inquires about her prognosis.*

### WHAT IS THE PROGNOSIS FOR PATIENTS WITH CHRONIC HCV INFECTION?

A detailed discussion of the natural history of chronic HCV infection can often allay patient fears about the disease. Most patients with HCV infection are asymptomatic. Infection resolves in an estimated 15% to 40% of acutely exposed patients, while the remainder develop chronic infection, manifested by persistent presence of detectable virus in the serum. Of persons with chronic infection, 60% to 70% will have intermittently or persistently abnormal serum ALT levels (49). An early study of transfusion-related HCV infection showed no increase in mortality among infected persons; however, the control group in this study was patients undergoing cardiac surgery (53). Mortality prediction may be confounded by the route of transmission of HCV, which in itself may increase risk for morbidity. When retrospective and prospective data are combined, it is estimated that 15% to 20% of persons with HCV infection progress to cirrhosis and may ultimately die as a result of the infection, while approximately 5% of infected persons will ultimately develop hepatocellular carcinoma (1, 54). In one cohort of 131 blood-transfusion recipients, the mean times between exposure to HCV and the development of chronic HCV infection, cirrhosis, and hepatocellular carcinoma were 13.7, 20.6, and 28.3 years, respectively (1).

Several recent longitudinal studies, including a cohort study of 376 Irish women infected by contaminated Rh-factor immunoglobulin and a study of 8568 U.S. military recruits, have suggested that persons who are infected at a young age may have a better long-term prognosis (55, 56). Regardless of the absolute rates, several factors are known to increase the risk for fibrotic

progression. Older patients, those who consume more alcohol, and those who present with more advanced histologic fibrosis on analysis of initial liver biopsy have higher rates of fibrotic progression (1, 57, 58). Patients with persistently normal levels of serum ALT have a lower risk for fibrotic progression (59). Although the natural history of HCV infection remains controversial, researchers would agree that the disease causes progression to clinically significant liver disease in a large portion of infected patients.

*The patient asks if her husband of 24 years is at risk for the infection. He claims to have no known risk factors. The husband and wife have been monogamous for 26 years and have two children, aged 20 and 22 years, who appear to be in good health.*

### DO PATIENTS WITH CHRONIC HCV INFECTION PRESENT A RISK TO THEIR SEXUAL PARTNERS, CHILDREN, OR OTHER HOUSEHOLD CONTACTS? SHOULD THESE PERSONS BE TESTED FOR HCV INFECTION?

Although initial reports of the epidemiology of HCV infection showed a significant risk for sexual transmission, recent studies are more equivocal (60). Cross-sectional studies report a 1% to 3% lifetime risk for infection in sexual partners of patients with known HCV infection. Although few prospective studies have been reported on this subject, the risk for sexual transmission of HCV should be considered low but present. Such risk appears to be increased by HCV–HIV coinfection (61). The U.S. Centers for Disease Control and Prevention does not currently recommend a change in the sexual practices of monogamous couples in which one partner is chronically infected with HCV (50).

The reported estimated risk for mother-to-infant transmission of HCV infection has varied widely, ranging from 0% to 20%. In a recent large prospective analysis of 15 250 pregnancies in which transmission was defined as persistent viremia in infants 1 year of age, the risk for vertical transmission was found to be 5.1%. Previous studies may have overestimated the rate of vertical transmission because of persistent maternally derived antibodies found in the infants during the first year of life (50). On the basis of the available evidence, the Centers for Disease Control and Prevention currently recommends testing children born to women

with HCV infection no earlier than 12 months of age. Immunoglobulin is not recommended as a means of prophylaxis (49). Breast feeding by women with chronic HCV infection is not thought to constitute a substantial health risk to the baby (51, 62). In general, routine testing of children of women with chronic HCV infection is not recommended because of the low risk for vertical transmission, the lack of information on persistent viremia rates in children with vertical transmission and the natural history of their infections, and the lack of data on and experience in using interferon-based regimens in pediatric patients.

In the hypothetical case described in this paper, the patient's children, who are now adults, should be encouraged to inform their physicians of their mother's infection. Other risk factors should be elucidated. Ultimately, the decision to undergo testing will be a personal one.

To date, no cases of nonsexual household transmission of HCV infection have been reported. Patients are advised to avoid sharing toothbrushes, razors, and nail-care tools because of the potential risk for parenteral exposure. A single case report has described HCV infection transmitted in the setting of home infusion therapy for hemophilia (62); however, in general, patients should be reassured that HCV transmission during normal household events is extremely uncommon.

*The patient's husband tests negative for HCV. Her children have been contacted and are considering their options. The patient asks whether there are nutritional or preventive approaches to minimize the impact of her chronic HCV infection. The patient reports having one to two glasses of wine with dinner each night and asks whether this is harmful.*

#### IS THERE EVIDENCE SHOWING THAT MODIFICATION OF HEALTH BEHAVIORS AND DIET AFFECTS THE COURSE OF CHRONIC HCV INFECTION?

Alcohol intake is undoubtedly a cofactor in the rate of progression of chronic HCV infection. Poynard and colleagues (63) demonstrated that consumption of more than 50 g of alcohol per day is associated with more fibrosis in liver biopsies of patients with HCV infection. (A standard mixed drink, a 12-oz beer, and a 4-oz glass of wine each contain approximately 10 g of alcohol.) The risk for cirrhosis and hepatic decompensation increases with alcohol consumption exceeding 60 g/d in

men and 40 g/d in women (58). Furthermore, alcohol intake tends to increase hepatitis C viral loads and to decrease responsiveness to interferon-based therapy (64, 65). On the basis of these data, it is advisable for patients to abstain from or limit alcohol consumption.

Most persons with HCV infection have retained liver synthetic function; thus, no specific dietary recommendations can be made. A single epidemiologic investigation (66) suggested an association between higher lipid intake and increased risk for cirrhosis in persons infected with HCV; however, there is no basis for recommending routine restriction of protein, carbohydrates, or fats for the specific indication of chronic HCV infection.

*The patient inquires about further testing and treatment, and asks to be referred to a specialist in gastroenterology and hepatology.*

#### WHEN SHOULD GENERALISTS REFER PATIENTS WITH CHRONIC HCV INFECTION TO SUBSPECIALISTS?

All patients with chronic HCV infection who are healthy enough to be considered for antiviral therapy should be evaluated by a physician with experience in the use of interferon-based regimens. This will usually be a gastroenterologist or hepatologist. Even patients who report a lack of interest in pharmacologic therapy may benefit from such a consultation, which can provide them with more information about natural history, diagnosis, and therapeutic options. Patients with advanced liver disease should be referred to a center that can evaluate for and perform liver transplantation.

*After performing a detailed history and physical examination, the specialist orders quantitation of HCV RNA with viral genotyping, serologic tests for HAV and HBV, antinuclear antibody tests, and tests for thyroid-stimulating hormone levels. The patient is noted to have genotype 1a and a viral load of 600 000 IU/mL. Serologic tests reveal no previous exposure to HAV or HBV. Test results for antinuclear antibody are negative, and the level of thyroid-stimulating hormone is normal. After conferring with the primary care physician, the specialist schedules a liver biopsy.*

#### WHEN IS LIVER BIOPSY INDICATED IN THE EVALUATION OF HCV INFECTION?

Most hepatologists prefer to include an examination of liver histology in the management of patients with

**Table 3. Treatment of Hepatitis C Virus Infection**

Treatment	Sustained Virologic Response	Sustained Virologic Response in Genotype 1	References
	%		
Interferon- $\alpha$	10 to 20	5 to 10	87
Interferon plus ribavirin	35 to 40	15 to 30	11
Pegylated interferon	23 to 39	30*	81–83
Pegylated interferon plus ribavirin	54	40*	84, 85

\* Values are approximate.

chronic HCV infection (67). Random core biopsy analysis reveals information about the inflammatory grade and fibrotic stage of chronic HCV infection.

*The patient undergoes liver biopsy without complication. The hepatic histology is consistent with mild HCV infection: Inflammation is limited to the portal tracts, and no fibrosis is seen.*

### HOW SHOULD FINDINGS ON LIVER BIOPSY GUIDE THE THERAPEUTIC RECOMMENDATION?

In patients with mild inflammation and no significant fibrotic change, treatment is less urgent because risk for progressive liver disease is lower. The presence of severe inflammation or bridging fibrosis should serve as an impetus for therapy. Histologic evaluation of the liver also aids in guiding the therapy of patients who do not respond to antiviral treatment. In persons with milder disease, further therapy can be deferred until more effective treatment regimens are developed. For patients whose biopsy findings reveal more advanced disease, longer treatment times, maintenance therapy, and enrollment in clinical trials should be considered more seriously. Patients with a persistently normal ALT level (approximately 25% of all chronically infected patients) may have substantial inflammation or fibrosis on liver biopsy (68). Antiviral therapy should be considered in such patients, especially in the setting of a randomized clinical trial.

As rates of sustained virologic response improve with evolving interferon-based therapies, liver biopsy may become recommended only in those patients whose pretreatment characteristics predict the lowest success rates. If patients with positive predictors of virologic response, such as low viral load and infection with genotype 2 or 3, can be treated and have very high chances of response, a biopsy that reveals mild histologic changes may do little to dissuade the clinician and patient from

immediate treatment. Currently, expert opinions regarding treatment of patients with mild histologic changes vary considerably. In this setting, a frank discussion of the positive and negative aspects of HCV therapy, along with consideration of the patient's preferences, should contribute to such decisions.

*The patient returns to her primary care physician after the consultation. The consultant has suggested peginterferon-ribavirin combination therapy and vaccination against HAV.*

### WHAT ARE THE PHARMACOLOGIC THERAPEUTIC OPTIONS FOR CHRONIC HCV INFECTION?

Offering vaccination against HAV for this patient is appropriate. Although HAV infection does not lead to chronic hepatitis, acute infection in adults and in persons with underlying chronic HCV infection results in high morbidity and mortality (69, 70). Hepatitis A vaccine, which has been shown to be safe and effective in patients with underlying chronic HCV infection, may prevent such poor outcomes (71). The cost-effectiveness of vaccinating all patients with chronic hepatitis against HAV has been questioned (72, 73), but the Advisory Committee on Immunization Practices (74) recommends such vaccination in persons with HCV infection who have evidence of chronic liver disease.

The goal of HCV therapy has been the long-term eradication of detectable virus in the serum. Sustained virologic response, the usual standard of successful therapy, is defined as the absence of HCV RNA in the serum during therapy and 6 months after the completion of therapy. Type 1 interferons have been the mainstay of HCV therapy since their approval for the treatment of non-A, non-B hepatitis in 1991 (75). Experimentation with dose and duration of therapy has done little to improve poor response rates (76). In 1998, the FDA approved the combination of interferon and

the nucleoside analogue ribavirin for patients with chronic HCV infection. This combination, known as Rebetron (Schering Corp., Kenilworth, New Jersey), improved sustained virologic response to approximately 40%, with higher rates observed in patients infected with HCV genotype 2 or 3 (11). When this combination was used in patients who had relapse of hepatitis after initially successful interferon monotherapy, 49% had sustained virologic response (77). Among previous nonresponders to interferon monotherapy, sustained virologic response rates with combination therapy have ranged from 10% to 30% (78). Retrospective analysis of data from large clinical trials has suggested that response rates are significantly higher in patients who receive more than 80% of the recommended dosage of interferon and ribavirin for more than 80% of the recommended duration of therapy (the so-called “80/80/80 rule”). This approach has yet to be prospectively validated (79).

The cost-effectiveness of antiviral therapy for chronic HCV infection has been formally analyzed. Interferon–ribavirin combination therapy for 24 and 48 weeks prolongs life expectancy at marginal cost-effectiveness ratios of \$4400 to \$7700, respectively, per discounted quality-adjusted life-year gained (80). This cost compares favorably with that of many commonly accepted medical interventions, such as hypertension treatment and breast cancer screening (80).

Analysis of the pharmacokinetics of intermittently dosed subcutaneous interferon has suggested that the standard regimen of three times per week is suboptimal. An optimized interferon molecule would allow a more stable serum interferon level rather than the peaks and troughs that characterize the serum levels of currently available interferons. Such pharmaceuticals have been developed by attaching a polyethylene glycol moiety to type 1 interferons (pegylation). One such pegylated interferon has recently been approved for clinical use in the United States, and another is being reviewed by the FDA. Randomized clinical trials have shown increased efficacy of pegylated interferon compared with standard interferons in cirrhotic and noncirrhotic patients with chronic HCV infection (81–83). In vitro evidence demonstrates the same synergy with ribavirin as is seen with standard interferon therapy (84). Peginterferon in combination with ribavirin has become the de facto standard of care for treatment of chronic HCV infection since

multicenter trials demonstrated a sustained virologic response of 54%. In subgroup analysis, sustained virologic response was 42% in patients infected with genotype 1 and was 82% in patients infected with genotype 2 or 3 (85).

In the case described in this paper, the consultant and primary care physician should discuss with the patient the evidence for efficacy of antiviral therapy and should offer her combination therapy with peginterferon plus ribavirin. Many hepatologists would encourage patients like this one to opt for treatment. Clinicians should be aware, however, that viral response rates in the community practice setting may be lower than published rates (86). **Table 3** summarizes the historical and current antiviral approaches to the treatment of chronic HCV infection.

#### WHAT ADVERSE EFFECTS OCCUR WITH ANTIVIRAL THERAPY FOR HCV INFECTION?

Side effects of interferon therapy include myalgias, fever, nausea, irritability, and depression. Treatment dropout rates were approximately 20% in initial trials, but subsequent experience with dose reduction has seen this rate decrease to approximately 10%. Hemolytic anemia, with an expected hemoglobin decrease of 10 to 30 g/L, is a ubiquitous side effect of ribavirin that reverses with cessation of therapy. Dose adjustment of ribavirin may be necessary in patients with excessive decreases in hematocrit (11).

**Table 4. Contraindications to Interferon-Based Therapy\***

Therapy	Contraindication	
Interferon	Decompensated liver disease	
	Severe psychiatric disease, especially severe depression	
	Autoimmune disease	
	Active substance abuse, including alcohol	
	Pregnancy	
	Comorbid disease	
	Unstable coronary artery disease	
	Uncontrolled seizure disorder	
	Uncontrolled diabetes	
	Uncontrolled hypertension	
	Interferon plus ribavirin	Anemia
		Hemolysis
Renal insufficiency		
Coronary artery disease		
Cerebral vascular disease		
Gout		
Inability to practice contraception		

\* Adapted from reference 88 with permission from Harcourt, Inc.

### WHAT ARE THE CONTRAINDICATIONS TO ANTIVIRAL THERAPY FOR HCV INFECTION?

When used alone or in combination with ribavirin, interferon can worsen depression, exacerbate autoimmune disease, suppress bone marrow, and cause mood disturbances. Ribavirin may also cause hemolytic anemia, which can be profound in patients with renal insufficiency or underlying hemolytic states. Furthermore, anemia can exacerbate preexisting significant cardiovascular disease. Table 4 lists contraindications to interferon-based therapies.

*After discussing the situation with her family, primary care physician, and consulting gastroenterologist, the patient decides to forgo interferon-based therapy, citing the low response rates, potential side effects, and her mild histology. She says that she prefers to explore complementary and alternative approaches to management of HCV infection.*

### DOES EVIDENCE SUPPORT THE USE OF COMPLEMENTARY AND ALTERNATIVE THERAPIES IN THE MANAGEMENT OF CHRONIC HCV INFECTION?

Many practitioners have noted frequent use of complementary and alternative medicine in their patients with chronic liver disease. Recently presented interview data revealed that 36% of patients with chronic HCV infection were taking herbal preparations (89). One third of those users were doing so without the knowledge of their physicians. The most commonly used herbs were milk thistle (and its ingredient, silymarin), St. John's wort, *Ginkgo biloba*, ginseng, and echinacea (89–92). Anecdotal evidence suggests widespread use of silymarin compounds among patients with diagnosed HCV infection. Animal and in vitro studies with silymarin have demonstrated its protective effect against a variety of known hepatic irritants, including bile duct occlusion, hepatic ischemia, alcohol, iron, acetaminophen, carbon tetrachloride, and phalloidin toxin extracted from *Amanita phalloides*. The effects of silymarin are assumed to be related to antioxidant and hepatoprotective properties. No cases of silymarin toxicity have been reported (93). Because no credible data exist on the efficacy of the alternative compounds, patients should be cautioned about their use.

*The patient returns for a routine office visit 6 months later. She has limited her alcohol intake, is taking antioxidant preparations, and feels well. She asks about the*

*appropriate interval and nature of follow-up visits for her chronic HCV infection and inquires about new therapeutic developments.*

### HOW OFTEN SHOULD CLINICIANS SEE UNTREATED PATIENTS WITH HCV INFECTION? WHAT FOLLOW-UP STUDIES ARE RECOMMENDED?

Because neither aminotransferase levels nor viral load measurement accurately gauges the progression of HCV infection, the only meaningful way to monitor patients for evidence of fibrotic progression is through histologic examination. An interval of 3 to 5 years for liver biopsies in untreated patients is widely recommended (34). As more effective therapies develop, this “watchful waiting” strategy may be replaced by more widespread antiviral treatment in patients with mild disease (94).

Other promising approaches to current clinical challenges and those yet to come include development of a vaccine; inquiries into the pathways involved in inflammation and fibrogenesis; and development of protease, polymerase, and helicase inhibitors. Perhaps of greatest importance, identification of persons with HCV infection and decreased risk for further transmission will reduce the future disease burden from this common infection (95–100).

### SUMMARY

Chronic HCV infection is a growing health concern in the United States. Although the incidence of new infections is decreasing, the burden of this infection on the health care system is expected to sharply increase over the coming decades. Identification of infected persons requires a high index of suspicion. Therapy is currently most highly recommended for patients with the highest risk for progression; however, as the tolerability and efficacy of antiviral agents improve, the threshold for treatment will become lower. The primary care physician plays a vital role in identifying patients chronically infected with HCV, educating patients about risk factors for transmission, advising patients against alcohol use, and aiding patients in making treatment decisions.

### APPENDIX: RECOMMENDED ELECTRONIC SOURCES OF INFORMATION ON HCV INFECTION

“Chronic Hepatitis C: Current Disease Management,” from National Digestive Diseases Information Clearinghouse (NDDIC), a service of the U.S. National Institute of Diabetes and Digestive

and Kidney Diseases (NIDDK). Available at [www.niddk.nih.gov/health/digest/pubs/chrnhepc/chrnhepc.htm](http://www.niddk.nih.gov/health/digest/pubs/chrnhepc/chrnhepc.htm).

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“Get tested for hepatitis C,” from the Centers for Disease Control and Prevention, directed toward patients concerned about risk factors for HCV infection. Available at [www.cdc.gov/ncidod/diseases/hepatitis/c/lbtinfo.htm](http://www.cdc.gov/ncidod/diseases/hepatitis/c/lbtinfo.htm). Also available in Spanish at [www.cdc.gov/ncidod/diseases/hepatitis/c/lbtinfo-sp.htm](http://www.cdc.gov/ncidod/diseases/hepatitis/c/lbtinfo-sp.htm).

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