Published in final edited form as:

Ann Intern Med. 2008 June 03; 148(11): ITC6-1-ITC6-16. doi:
10.7326/0003-4819-148-11-200806030-01006.

In the clinic. Hepatitis C

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Abstract

Chronic hepatitis C virus (HCV) infection is the most common blood-borne infection in the United States, with an estimated overall prevalence of 3.2 million persons (1.3%) and prevalence peaks between age 40 to 49 years (1). The worldwide prevalence of HCV infection is even higher at 2.0%, corresponding to 140 million persons (2).

In terms of complications, cirrhosis due to HCV disease is the most frequent indication for liver transplantation in the United States (3), and the overall incidence of hepatocellular carcinoma, a complication of HCV cirrhosis, continues to increase at alarming rates. In an evaluation of population-based registries of the Surveillance, Epidemiology, and End Results (SEER) program in the United States, the overall age-adjusted incidence rates of hepatocellular carcinoma increased from 1.4 per 100 000 in 1975 to 1977 to 3.0 per 100 000 in 1996 to 1998 (4).

Prevention

What factors increase the risk for hepatitis C virus (HCV) infection?

The predominant risk factor for the transmission of HCV is percutaneous exposure to infected blood, which most commonly takes place through remote or chronic injection drug use. Transmission of HCV historically occurred with transfusion of blood products before screening of the blood supply in the United States before 1992. There seems to be no increased risk for HCV transmission through cosmetic procedures, such as tattooing and piercings, unless infection control measures are not followed (5).

Transmission of HCV in health care workers after a needle-stick exposure occurs in up to 10% of cases (6). Additionally, the prevalence of HCV infection in hemodialysis patients is

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For More Information

Centers for Disease Control and Prevention (CDC)

Hepatitis C Prevention www.cdc.gov/ncidod/diseases/hepatitis/c/hepcprev.htm

Viral Hepatitis C www.cdc.gov/ncidod/diseases/hepatitis/c/index.htm

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Chronic Hepatitis C: Current Disease Management digestive.niddk.nih.gov/ddiseases/pubs/chronichepc/index.htm

What I Need to Know about Hepatitis C digestive.niddk.nih.gov/ddiseases/pubs/hepc_ez/index.htm (English) digestive.niddk.nih.gov/spanish/pubs/hepc_ez/index.htm (Spanish)

approximately 8.9% in the United States, with higher rates in developing countries (7). Nosocomial outbreaks have also been reported to be related to failures in infection control, such as reuse of needles and syringes as well as multidose vials and saline bags to make flushes (8).

Sexual intercourse is another mode of HCV transmission, but persons in long-term monogamous partnerships have a lower risk (0% to 0.6% per year) than persons with multiple partners or those at risk for sexually transmitted infections (0.4% to 1.8% per year) (9). Mother-to-child transmission in the presence of HCV viremia in the mother is approximately 4% to 7%. However, the risk for HCV transmission to the neonate increases up to 4- to 5-fold when the mother has both HCV and HIV infection (10).

How can individuals, including those who live with an infected individual, reduce their risk for HCV infection?

Avoidance of high-risk behaviors is the mainstay of risk reduction in HCV. Treatment programs or needle-exchange programs should be considered if available for persons injecting drugs. These programs have demonstrated reductions in high-risk practices, such as sharing needles, but the evidence has been less convincing for reductions in HCV transmission (11).

A recent study of a Dutch cohort of 714 injection drug users found that the combination of a methadone program and a needle-exchange program led to a decreased risk for HIV seroconversion (incidence rate ratio, 0.43 [95% CI, 0.21 to 0.87]) and HCV (incidence rate ratio, 0.36 [CI, 0.13 to 1.03]) when compared with no treatment (12).

Individuals infected with HCV who have multiple sexual partners should be advised to use condoms to prevent transmission of HCV and other sexually transmitted infections (3) (Monogamous couples should also be advised that condoms may reduce the risk for transmission, but they are not routinely recommended because of the low risk for sexual transmission in this situation). The exact risk for horizontal transmission of HCV to household contacts of individuals with active HCV infection remains unclear, but avoiding sharing razors, toothbrushes, and nail clippers with an individual with chronic HCV infection is recommended. Although this advice was initially based on general recommendations for preventing transmission of blood-borne infections (13), samples from toothbrushes from infected individuals have been shown to contain HCV RNA (14), and sharing of razors has been found to be an independent risk factor for HCV infection (15).

How can risk for HCV infection be reduced in the health care setting?

Health care workers and volunteers should follow appropriate infection control practices to decrease their personal risk for infection and to reduce the risk for spreading HCV from one patient to another. For example, health care workers should never reuse a needle or syringe from another patient to withdraw medicine from a vial or bag of intravenous fluids. Medicines in multidose vials may present a particular risk, and a new needle and clean syringe should always be used to access the medication from such containers (16).

Prevention

The most significant risk factor for acquiring HCV infection is percutaneous exposure, historically through transfusion of blood products and now most commonly through injection drug use. Although sexual transmission risk is low and condom use is not routinely recommended for monogamous couples, it is recommended for HCV-positive patients with multiple sex partners. Sharing razors, toothbrushes, and nail clippers should be avoided. Infection control practices are critical to reduce the risk to health care workers and among patients in health care settings.

Risk Factors for HCV Infection

- Injection drug use (past or present)
- Receipt of clotting factor concentrates produced before 1987
- Long-term hemodialysis treatment
- Repeatedly elevated (or unexplained intermittently elevated) serum alanine aminotransferase levels
- Receipt of blood or blood components (for example, red cells, platelets, fresh-frozen plasma) or solid-organ transplants before July 1992
- Receipt of blood from an HCV-positive donor
- Specific high-risk exposure to known HCV-positive blood in health care workers, (e.g., needle-sticks or other sharp exposure or mucosal exposure [splash accidents])
- HIV infection
- Being the child of HCV-positive woman
- History of multiple sex partners or sexually transmitted infections
- Sharing razors

Screening

Should clinicians screen patients for hepatitis C infection?

In 2004, the U.S. Preventive Services Task Force concluded that there were inadequate data to recommend screening healthy asymptomatic adults for hepatitis C infection. The report highlighted the lack of published trials of screening for HCV infection and the absence of data that treatment improved long-term outcomes (17).

This recommendation was strongly challenged by members of the national societies of gastroenterology and hepatology, who felt that, because of the long natural history of HCV infection, it would be inappropriate to wait several decades to be able to prove the benefit of screening. They emphasized that treatment must be provided before the onset of

complications of cirrhosis and recommended continued screening of persons with risk factors for HCV infection (Box) (18).

What test should clinicians use when screening for hepatitis C infection?

The test of choice to screen for HCV infection is the antibody to HCV by enzyme-linked immunosorbent assay (ELISA). Performed with second- or third-generation assays, the ELISA has a sensitivity of 98.9% to 100% and a specificity of 99.3% to 100% (19).

Screening

Although long-term studies have not clearly demonstrated the overall benefits and risks of screening in healthy asymptomatic adults, current guidelines from the gastroenterology and hepatology professional societies recommend screening persons with risk factors (for example, injection drug use, multiple sex partners, or a history of sexual transmitted infections) for HCV infection with HCV antibody by ELISA.

Diagnosis

What is the clinical spectrum of hepatitis C infection?

At the time of acute infection with HCV, most individuals are asymptomatic. Among symptomatic patients with acute infection, jaundice may occur, but the presentation is more commonly nonspecific with fatigue, nausea, abdominal pain, or flu-like symptoms. Acute liver failure due to HCV infection is very uncommon. Chronic infection develops in 74% to 86% of exposed patients over time, during which patients usually remain asymptomatic. Most patients with chronic HCV infection present with abnormal liver tests, although many may have normal alanine aminotransferase levels and up to 20% of those with normal levels may have significant fibrosis on liver biopsy (20).

Cirrhosis develops in 15% to 20% of chronically infected patients, although natural history data are limited given the prolonged course of disease and the small number of prospective cohort studies. Patients with cirrhosis may then progress to develop the complications of portal hypertension. The risk for hepatocellular carcinoma is up to 3% per year among patients with cirrhosis (3). Those with advanced disease have fatigue, jaundice, lower extremity edema, ascites, altered mental status due to hepatic encephalopathy, or gastrointestinal bleeding from varices or portal gastropathy. Additional findings of chronic liver disease, such as splenomegaly, spider angiomas, caput medusae, and gynecomastia, may be seen. An abdominal mass in a patient with anorexia and weight loss suggests HCV-related hepatocellular carcinoma.

Patients with HCV infection may present with manifestations of other related disorders (Box).

In a series of 321 patients, 38% had at least 1 extrahepatic manifestation of HCV infection, including arthralgia, skin manifestations, xerostomia, xerophthalmia, and sensory neuropathy. Mixed cryoglobulins were found in 56% of patients, and at least 1 autoantibody was found in 70% (21).

What laboratory tests should clinicians use to diagnose hepatitis C infection?

A positive antibody to HCV by ELISA should prompt measurement of HCV RNA by polymerase chain reaction to confirm chronic infection. Quantitative HCV RNA viral load should be obtained to serve as a baseline, although there is poor correlation between viral load and hepatic histology. For those with detectable viral loads, HCV genotype should be obtained in any patient being considered for therapy, because genotype affects likelihood of treatment response and duration of therapy (22). Specific genotypes are more prevalent in different areas of the world (Box). Most other liver function studies lack specificity, and other laboratory tests should be reserved for patients with evidence of cirrhosis or extrahepatic manifestations of HCV infection (Table 1).

When should clinicians consider liver biopsy?

Once HCV infection has been confirmed with HCV RNA testing, clinicians should consider the potential value of additional information afforded by liver biopsy. Given the significant side effects and modest response rates in genotypes 1 and 4 associated with drug treatment, clinicians may decide to recommend biopsy to help identify patients at greatest risk for disease progression. In this case, patients with moderate-to-severe fibrosis on liver biopsy should be considered for treatment, whereas patients with minimal or no fibrosis on liver biopsy may defer treatment given the slow natural history of HCV infection and the minimal risk for complications in the early stages of disease. However, even in patients with normal alanine aminotransferase levels, liver biopsy may demonstrate the presence of significant fibrosis, a finding that would lead to consideration of therapy (24). Biopsy can also help clinicians assess the risk versus benefit of treatment in patients with relative contraindications to therapy. Liver biopsy may thus be a helpful tool in making treatment decisions, and repeated determination of hepatic histology over time is useful to decrease sampling error and estimate rate of progression. However, liver biopsy should not be an absolute requirement in the evaluation process for patients who desire treatment regardless of biopsy findings (3). Moreover, some have suggested that liver biopsy is not necessary in genotype 2 or 3 infection given the higher response rates to treatment.

What other hepatic conditions have clinical presentations similar to hepatitis C infection?

Because the symptoms and laboratory abnormalities associated with HCV infection are nonspecific, and infected individuals are most often asymptomatic, the differential diagnosis of HCV-related liver disease is particularly broad. Any liver disease causing mild-to-moderate elevations in levels of transaminases or cirrhosis should be considered (Table 2). In addition, HCV infection can occur in patients with other liver diseases; therefore, additional testing may be warranted.

Diagnosis

Chronic HCV infection is usually asymptomatic, and most patients present with abnormal liver function tests. The diagnosis may also be suggested by extrahepatic manifestations or signs and symptoms of portal hypertension or hepatocellular carcinoma. Diagnosis is suggested with the antibody to HCV by ELISA and confirmed

with the HCV RNA by polymerase chain reaction. Clinicians should consider liver biopsy to evaluate the degree of fibrosis and guide treatment decisions.

Extrahepatic Manifestations of HCV Infection

- Arthritis
- Porphyria cutanea tarda
- Leukocytoclastic vasculitis
- Lichen planus
- Raynaud phenomenon
- The sicca syndrome
- Idiopathic thrombocytopenic purpura
- Membranoproliferative glomerulonephritis
- Membranous nephropathy
- Hypo/hyperthyroidism
- Diabetes mellitus
- Essential mixed cryoglobulinemia
- Monoclonal gammopathy
- Non-Hodgkin lymphoma

Prevalence of Genotypes in Different Areas

1a	Northern Europe, United States
1b	Global, Southern Europe
2	Europe, North Africa
3	Southeast Asia
4	Middle East
5	South Africa
6	Asia

Treatment

Are dietary and other lifestyle interventions helpful in the management of hepatitis C infection?

Alcoholic liver disease often complicates HCV-related liver disease. The presence of cirrhosis has been shown to be hastened by increased alcohol consumption in HCV-infected individuals, and abstinence from alcohol is therefore recommended (25).

Hepatotoxic drugs should clearly be avoided in patients with any liver disease. Use of acetaminophen in normal doses is not contraindicated, but clinicians and patients should be aware of the danger of intentional or accidental overdose through heavy use of multiple analgesics containing acetaminophen (26). Similar care should be taken with non-steroidal anti-inflammatory drugs, which are particularly risky in patients with cirrhosis.

A low-sodium diet is recommended for patients with cirrhosis and ascites complicating HCV infection, but no specific dietary interventions are necessary at earlier stages of disease. Protein restriction should be avoided in patients with cirrhosis.

Are complementary-alternative therapies useful in the treatment of patients with hepatitis C infection?

According to the evidence, herbal remedies, such as milk thistle, do not improve the outlook for HCV infection.

A systematic review of randomized clinical trials in patients with alcoholic liver disease, hepatitis B infection, and HCV determined that the overall methodological quality of trials was low. Although milk thistle was not associated with a statistically significantly increased risk for adverse events (RR, 0.83; CI, 0.46 to 1.50), it had no statistically significant effect on mortality (RR, 0.78; CI, 0.53 to 1.15), complications of liver disease (RR, 0.95; CI, 0.83 to 1.09), or liver histology (27).

In the case of milk thistle, no significant harm has been observed in studies to date (27). However, a number of herbal remedies, such as chaparral, leaf germander, jin bu huan, kava kombucha mushroom, margosa oil, mistletoe, pennyroyal, pyrrolizidine alkaloids, and traditional Chinese herbs, are known to be hepatotoxic (28). Patients with HCV infection should avoid using these remedies.

When should clinicians consider drug therapy for hepatitis C infection?

Clinicians should consider antiviral therapy in any patient who has no absolute contraindications (Box) for treatment, compensated liver disease (absence of ascites and encephalopathy), and detectable serum HCV RNA, especially if they have clinical or histologic signs of progression. Treatment for HCV is safe in patients with compensated cirrhosis; however, the presence of advanced fibrosis or cirrhosis is associated with decreased treatment response.

An alternative strategy is to perform periodic liver biopsies to assess progression of liver disease. Although there are no data to indicate the appropriate interval between liver

biopsies, pending better evidence the consensus of opinion is that every 3 to 5 years is reasonable.

Although the effects of the 2 strategies (biopsy versus empirical treatment) have not been compared in randomized trials, both have merit given the substantial side effects of drug treatment for HCV disease and the modest response rates. Each individual patient therefore requires thorough evaluation and discussion of the risks and benefits of treatment (3).

What are the contraindications to drug therapy for hepatitis C infection?

Contraindications to HCV therapy are listed in the Box. Ribavirin is contraindicated in pregnancy because of its teratogenicity. Ribavirin is cleared by the kidney, and its side effects, including hemolysis, can be severe in patients with renal insufficiency or those on hemodialysis. Treatment with interferon- α compounds has been associated with severe neuropsychiatric side effects, including suicide. Therefore, patients with a history of depression should be considered for HCV treatment only with close monitoring for exacerbation of psychiatric symptoms during treatment (3).

The most recent National Institutes of Health Consensus Conference Statement did not include active alcohol and illicit drug use as contraindications, and this remains an area of controversy. Alcohol use is associated with a decreased response rate to therapy, and cessation of alcohol use before initiation of drug therapy for hepatitis C infection should thus be encouraged. Formal alcohol treatment programs should be considered in patients who abuse alcohol.

A systematic review indicates that patients with HCV infection who abuse alcohol develop more severe fibrosis, cirrhosis, and hepatocellular cancer than nondrinkers. They have a lower rate of response to drug treatment with interferon as a result of nonadherence (29).

Small studies have demonstrated the feasibility and effectiveness of HCV treatment in patients in methadone programs and in those using illicit injection drugs. Patients actively using drugs should therefore be considered on a case-by-case basis by HCV infection treatment programs with appropriate multidisciplinary resources (3).

Clinicians should strongly consider antiviral therapy in patients with both HIV and HCV infection. With improved survival in HIV-infected patients in the past decade, complications of chronic liver disease have become more common among these patients (30). Although increased rates of acute pancreatitis and lactic acidosis were initially reported in patients treated with highly active antiretroviral treatment regimens containing didanosine along with ribavirin (31), a meta-analysis of recent studies of pegylated interferon- α and ribavirin report sustained virologic response rates of 26% to 44% overall and 14% to 38% in patients with genotype 1 with low incidence of pancreatitis and lactic acidosis (32). Pegylated interferon- α -2 α combined with ribavirin is approved by the U.S. Food and Drug Administration for treatment of patients co-infected with HIV and HCV.

Which drugs are effective in the treatment of hepatitis C infection, and how should clinicians choose from among available treatment regimens?

The optimal treatment in previously untreated patients with hepatitis C infection is combination therapy with pegylated interferon- α and ribavirin (Table 3). Pegylated interferon- α is traditional interferon- α attached to a polyethylene glycol chain, which functions to decrease renal clearance, increase stability, and prolong action. The 2 currently commercially available preparations are pegylated interferon- α -2a and pegylated interferon- α -2b. A large prospective head-to-head trial comparing the 2 pegylated interferon- α preparations has recently been completed, and results are expected soon, but to date there is no compelling evidence of the superiority of one over the other. Subcutaneous injections of pegylated interferon- α are administered once weekly, and ribavirin is given by mouth in divided doses twice daily.

Genotype should determine the treatment duration and likelihood of response. Genotype 1 infection is most common in the United States and requires 48 weeks of therapy; genotypes 2 and 3 require 24 weeks of therapy and have much higher response rates (33). The standard dose of ribavirin for HCV genotype 1 is weight-based (800 to 1400 mg/d); however, the dose is fixed and lower (800 mg/d) for genotypes 2 and 3 (34) (Table 3). Both available pegylated interferons have been shown to be more effective than unmodified interferon- α in large, randomized trials.

In a prospective, randomized, controlled trial (RCT), 1121 patients with chronic HCV infection received 1 of 3 regimens: pegylated interferon- α -2a 180 μ g weekly plus daily ribavirin (1000 or 1200 mg, depending on body weight); pegylated interferon- α -2a plus daily placebo; or 3 million units of unmodified interferon- α -2b 3 times weekly plus daily ribavirin. Sustained virologic response (defined as the absence of detectable HCV RNA 24 weeks after cessation of therapy) was higher in patients receiving pegylated interferon- α -2a and ribavirin than among those who received unmodified interferon- α -2b plus ribavirin (56% vs. 44%; $P < 0.001$) or pegylated interferon- α -2a alone (56% vs. 29%; $P < 0.001$). Among patients with genotype 1 infection, the highest sustained virologic response (46%) occurred in the pegylated interferon- α -2a and ribavirin group (35).

In another prospective RCT, 1530 patients with chronic HCV infection received 1 of 3 regimens: high-dose pegylated interferon- α -2b (1.5 μ g per kilogram body weight), lower-dose pegylated interferon- α -2b (1.0 μ g per kilogram body weight) with ribavirin, and unmodified interferon- α -2b with ribavirin. In all genotypes, high-dose pegylated interferon- α with ribavirin led to an increased sustained virologic response (54%) compared with lower-dose pegylated interferon- α (47%) or unmodified interferon (47%) in combination with ribavirin. The sustained virologic response rate in patients with genotype 1 was 42% with higher-dose pegylated interferon- α -2b with ribavirin in contrast to those with genotype 2 or 3, in which the sustained virologic response rate was approximately 80% (36).

Factors associated with a higher sustained virologic response in these studies included genotypes other than 1, lower baseline HCV RNA, minimum fibrosis, lower body weight, and ethnicity (not African-American). Multiple studies have now shown that African-

Americans have a reduced response rate to HCV treatment, but approximately 25% of African-American patients will respond (37).

Which vaccinations should patients with hepatitis C infection receive?

Clinicians should question patients with HCV infection about previous vaccinations or exposure to hepatitis A (HAV) and hepatitis B (HBV). If exposure or vaccination or disease cannot be documented, anti-HBs should be measured, and if negative, the patient should receive the HBV vaccination series. The cost-benefit ratio may favor empirical HAV vaccination rather than measurement of antibody followed by vaccine if antibody is absent (38). All patients with HCV infection should receive the influenza vaccine annually (39), and patients with cirrhosis should also receive the pneumococcal vaccine (40). These vaccines should be administered regardless of whether the patient receives drug treatment for HCV infection.

What is the appropriate clinical management for patients who do not respond to hepatitis C therapy or who relapse after an initial response?

There are 2 main categories of suboptimal response to hepatitis C treatment: nonresponse and relapse. Nonresponders demonstrate little or no response to treatment, whereas relapsers have undetectable HCV RNA at the end of treatment but detectable levels in follow-up monitoring.

Currently, there are no approved treatments for patients who do not initially respond to pegylated interferon- α and ribavirin. When evaluating patients with previous relapse or nonresponse to therapy, it is critical to evaluate the previous course of therapy. If patients relapsed after standard interferon monotherapy or combination interferon- α with ribavirin, they may benefit from treatment with pegylated interferon- α and ribavirin. If patients were nonresponders, it is important to determine whether any deficiencies in the first treatment could be improved with the second course. If a patient was non-adherent during the first course of treatment, a second course might be considered if it is believed that the patient may be more adherent on repeat treatment. If the previous dosing of medicine was incorrect or if inappropriate dose reductions occurred, treatment could be considered again. Merely repeating the same course of therapy is very unlikely to benefit the patient unless there is a realistic possibility of improving on the previous treatment experience. Treatment decisions in nonresponders can be aided greatly by examination of liver histology.

For patients who do not respond or who relapse after standard treatment, referral to a hepatologist for consideration of alternative approaches to standard therapy or enrollment in clinical trials should be considered. One recent strategy in clinical trials has been long-term maintenance therapy to theoretically reduce the risk for cirrhosis and portal hypertension. Early results from these studies have demonstrated conflicting findings, and there is insufficient evidence at this point to support this approach (41). Direct antiviral therapies, such as protease and polymerase inhibitors, are in the early phases of clinical trials and thus are not approved for treatment of HCV disease (42). In view of early data suggesting viral resistance to these agents used as monotherapy, these medications are being administered in

combination with pegylated interferon- α and ribavirin, and results from these trials are expected over the next several years.

What are the side effects of hepatitis C drugs and how should clinicians manage patients who develop side effects?

Therapy for HCV puts patients at risk for substantial side effects and requires diligent monitoring. The most common side effects are listed in Table 4. Although practitioners often tolerate lower neutrophil counts because the risk for infection is low (43), the current labels for pegylated interferon- α recommend dose reduction when neutrophil counts are less than 750 cells/mL and consideration of discontinuation for counts less than 500 cells/mL. Doses should be reduced when patients develop thrombocytopenia and when hemoglobin levels are less than 10 g/dL. Efforts should be made to avoid dose reductions and interruptions in treatment because retrospective analyses have suggested that these events for both pegylated interferon- α and ribavirin are associated with lower treatment response (3).

Erythropoietin and granulocyte colony-stimulating factor therapies have been used to correct cytopenias associated with therapy. Erythropoietin has been associated with improved quality of life and ability to maintain higher ribavirin doses on treatment; however, no data can adequately demonstrate the clinical benefit on virologic response compared with the risk of this approach (44). In 2007, the U.S. Food and Drug Administration issued a Public Safety Advisory on the potential dangers of erythropoiesis-stimulating agents, and a black box warning was added to the labels of these drugs noting serious cardiovascular and arterial and venous thromboembolic events (45). In regard to the management of thrombocytopenia, therapy with thrombopoietin-receptor agonists is an exciting advance in the treatment of liver disease, especially in patients with portal hypertension and hypersplenism. Further studies regarding their use are needed (46).

How should clinicians evaluate the response to hepatitis C drug therapy?

Assessing HCV RNA titers is the mainstay of monitoring response to antiviral treatment. The goal of treatment is sustained virologic response, which means that the patient has undetectable HCV RNA for 6 months after cessation of therapy. A baseline viral load should be drawn at or just before initiation of therapy. In order to prevent patients from receiving long courses of therapy with little chance of response, retrospective analyses of randomized trials of patients with genotype 1 infection have suggested determining viral load at week 12 for early virologic response, defined as at least a 2-log reduction in HCV RNA compared with baseline. As a result, patients who do not achieve early virologic response should discontinue treatment. If patients achieve early virologic response, their next landmark is week 24, and HCV RNA should be undetectable by this time point, or treatment should be halted.

In a retrospective analysis of a large clinical trial database, 131 of 511 patients receiving pegylated interferon- α - 2b and ribavirin did not achieve early virologic response, and none of these patients went on to achieve sustained virologic response. Between 69% and 76% of patients did achieve this threshold, depending on the treatment regimen, and 67% to 80% achieved sustained virologic response (47).

More recently, there has been interest in measuring the viral load at 4 weeks to determine whether an individual has had a rapid virologic response, defined as an undetectable viral load at that time point. Whereas early virologic response assessment at 12 weeks has been studied and used in patients with genotype 1 infection, patients with genotype 1, 2, and 3 have been studied in clinical trials to determine whether treatment should be shortened or prolonged depending on the response at 4 weeks (48). These promising early studies require confirmation before changes are made in standard recommendations for monitoring.

Are there other drug regimens with documented effectiveness in the treatment of hepatitis C?

Unmodified interferon with or without ribavirin was previously used to treat HCV before pegylated interferon- α was introduced. Now the standard of care involves combination regimens that include pegylated interferon- α . However, monotherapy with pegylated interferon- α is used when there are contraindications to treatment with ribavirin, including renal insufficiency, hemoglobinopathies, and coronary or cerebral artery disease (49).

Is it possible to cure hepatitis C infection?

Hepatitis C infection is felt to be initially cured after achievement of a sustained virologic response. Although it is possible to have a relapse after a sustained virologic response, the likelihood is quite low. If sustained virologic response is achieved, at least 98% of patients maintain an undetectable viral load indefinitely, and maintenance of sustained virologic response for 2 years is synonymous with a cure of HCV infection (49). It should be emphasized, however, that antibody is not protective, and patients can be reinfected after successful therapy.

When is liver transplantation indicated for patients with hepatitis C infection?

Clinicians should refer patients with cirrhosis due to HCV infection for liver transplantation evaluation when their Model for End-Stage Liver Disease (MELD) score is 10 or greater following their first major complication of portal hypertension (for example, ascites, hepatic encephalopathy, or variceal bleeding). The MELD score is a logarithmic calculation derived from the patient's serum creatinine level, serum bilirubin level, and prothrombin time or international normalized ratio. The MELD score predicts survival in the next 3 months and leads to scores ranging from 6 (less ill) to 40 (gravely ill). The current organ allocation system for liver transplantation is based on the MELD score (50). Hepatocellular carcinoma is also an important indication for referral for liver transplantation.

What is the risk for hepatocellular carcinoma in patients with hepatitis C infection and should they undergo routine screening for this cancer?

Hepatocellular carcinoma complicating HCV infection typically develops in the setting of cirrhosis. The rate of occurrence is estimated at up to 3% per year after the development of cirrhosis (3). Practice guidelines recommend screening with ultrasonography every 6 to 12 months, although some of the data come from screening trials involving patients with chronic HBV disease (51).

In an RCT of 18 816 patients with HBV infection or history of chronic hepatitis in China, biannual screening with ultrasonography and α -fetoprotein was compared with no screening over a 20-year period. In the screened group, 32 people died from hepatocellular carcinoma compared with 54 in the control group, yielding rates of 83.2 per 100 000 and 131.5 per 100 000, respectively. The rate ratio for mortality was 0.63 (CI, 0.41 to 0.98) (51).

Serum α -fetoprotein has limited utility as a screening test but should be used if imaging is not available. Area under the receiver-operating curve analysis suggests that the optimal cutoff value is 20 ng/mL, but this level yields a sensitivity of only 60% (52).

When is specialty consultation indicated for patients with hepatitis C infection?

Referral to a hepatologist or infectious disease specialist is indicated if there are questions or concerns regarding the diagnosis or management of HCV infection. Distinguishing HCV infection from other or coexisting liver diseases, determining the need for liver biopsy, choosing the next steps in patients who did not respond to pegylated interferon- α and ribavirin, or evaluating for liver transplantation should also prompt referral.

Treatment

Clinicians should individualize decisions on treatment of hepatitis C infection on the basis of stage of disease, clinical and laboratory evaluation, and patient preference. Standard treatment for HCV infection consists of pegylated interferon- α and ribavirin with dose and duration determined by genotype. Treatment success is sustained virologic response, defined as undetectable HCV RNA levels 6 months after cessation of therapy. Treatment requires close monitoring for side effects and evaluation of virologic response to determine whether to discontinue treatment early in patients who are not responding. Patients who do not respond to standard treatment should consider consultation for evaluation and consideration of other treatment strategies. Patients with cirrhosis and MELD scores of 10 or greater and those with hepatocellular carcinoma should be referred for liver transplantation evaluation. All patients should be considered for vaccination for hepatitis A, hepatitis B, and influenza; patients with cirrhosis should receive the pneumococcal vaccination.

Contraindications to Antiviral Therapy with Pegylated Interferon- α and Ribavirin

- Uncontrolled major depression, particularly with past suicide attempts
- Autoimmune hepatitis or other autoimmune disorders, including thyroid disease
- Bone marrow, lung, heart, or kidney transplantation
- Severe hypertension, coronary heart disease, congestive heart failure, cerebral vascular disease, or other serious nonliver disorders likely to reduce life expectancy
- Renal insufficiency

- Noncompliance with office visits or medications
- Decompensated cirrhosis or hepatocellular carcinoma
- Pregnancy or inability to practice birth control methods
- Severe anemia, thrombocytopenia, or granulocytopenia

Practice Improvement

What do professional organizations recommend with respect to hepatitis C infection?

The American Association for the Study of Liver Diseases Guidelines of the Diagnosis, Management and Treatment of HCV, published in 2004, provide recommendations on laboratory testing and counseling for hepatitis C as well as initial treatment of various patient groups, including children and those with HIV co-infection, renal disease, or decompensated cirrhosis and those undergoing solid organ transplantation. Management of patients with acute HCV infection and those who are active drug users is also covered (53).

The American Gastroenterological Association Technical Review covers screening, natural history, and treatment of HCV in adults and children as well as patients with renal disease and HIV co-infection, those actively using injection drugs, and recipients of liver transplants. Other treatment groups requiring particular consideration are patients with extrahepatic disease, African-Americans, and those with hematologic disorders (49).

The National Institutes of Health has released a Health Consensus Development Conference Statement on the management of hepatitis C covering its natural history, prevention, diagnosis, and areas for future research (3).

The U.S. Department for Veterans Affairs has issued guidelines covering epidemiology, prevention, testing, and counseling, as well as management of HIV/HCV co-infection and complications of HCV infection (54).

The United States Preventive Services Task Force issued guidelines in 2004 indicating that there were insufficient data to recommend screening for HCV infection in healthy individuals (17).

What measures do stakeholders use to evaluate the quality of care for patients with hepatitis C infection?

The Center for Medicare & Medicaid Services has issued specifications for performance measures for its 2008 Physicians Quality Reporting Initiative (PQRI). These include 5 measures applicable to patients with hepatitis C. Two involve HCV RNA as part of initial evaluation in all patients 18 years and older with the diagnosis and again within 6 months before initiating treatment. A third measure mandates HCV genotype testing before starting treatment. Two additional measures deal with treatment. The first involves consideration of drug treatment with pegylated interferon and ribavirin, and the second with HCV RNA testing at 12 weeks from initiation of antiviral treatment.

References

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* 2006; 144:705–714. [PMID: 16702586]. [PubMed: 16702586]
2. Bialek SR, Terrault NA. The changing epidemiology and natural history of hepatitis C virus infection. *Clin Liver Dis.* 2006; 10:697–715. [PMID: 17164113]. [PubMed: 17164113]
3. National Institutes of Health. National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002—June 10–12, 2002. *Hepatology.* 2002; 36:S3–S20. [PMID: 12407572]. [PubMed: 12407572]
4. El-Serag HB, Davila JA, Petersen NJ, et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med.* 2003; 139:817–823. [PMID: 14623619]. [PubMed: 14623619]
5. Hwang LY, Kramer JR, Troisi C, et al. Relationship of cosmetic procedures and drug use to hepatitis C and hepatitis B virus infections in a low-risk population. *Hepatology.* 2006; 44:341–351. [PMID: 16871571]. [PubMed: 16871571]
6. Lanphear BP, Linnemann CC Jr, Cannon CG, et al. Hepatitis C virus infection in healthcare workers: risk of exposure and infection. *Infect Control Hosp Epidemiol.* 1994; 15:745–750. [PMID: 7534324]. [PubMed: 7534324]
7. Fabrizi F, Poordad FF, Martin P. Hepatitis C infection and the patient with end-stage renal disease. *Hepatology.* 2002; 36:3–10. [PMID: 12085342]. [PubMed: 12085342]
8. Macedo de Oliveira A, White KL, Leschinsky DP, et al. An outbreak of hepatitis C virus infections among outpatients at a hematology/oncology clinic. *Ann Intern Med.* 2005; 142:898–902. [PMID: 15941696]. [PubMed: 15941696]
9. Terrault NA. Sexual activity as a risk factor for hepatitis C. *Hepatology.* 2002; 36:S99–S105. [PMID: 12407582]. [PubMed: 12407582]
10. Roberts EA, Yeung L. Maternal-infant transmission of hepatitis C virus infection. *Hepatology.* 2002; 36:S106–S113. [PMID: 12407583]. [PubMed: 12407583]
11. Hagan H, Thiede H. Changes in injection risk behavior associated with participation in the Seattle needle-exchange program. *J Urban Health.* 2000; 77:369–382. [PMID: 10976611]. [PubMed: 10976611]
12. Amsterdam Cohort. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction.* 2007; 102:1454–1462. [PMID: 17697278]. [PubMed: 17697278]
13. Shapiro CN. Transmission of hepatitis viruses [Editorial]. *Ann Intern Med.* 1994; 120:82–84. [PMID: 8250462]. [PubMed: 8250462]
14. Lock G, Dirscherl M, Obermeier F, et al. Hepatitis C - contamination of toothbrushes: myth or reality? *J Viral Hepat.* 2006; 13:571–573. [PMID: 16907842]. [PubMed: 16907842]
15. Sawayama Y, Hayashi J, Kakuda K, et al. Hepatitis C virus infection in institutionalized psychiatric patients: possible role of transmission by razor sharing. *Dig Dis Sci.* 2000; 45:351–356. [PMID: 10711450]. [PubMed: 10711450]
16. Siegel, JD.; Rhinehart, E.; Jackson, M., et al. the Healthcare Infection Control Practices Advisory Committee. [on 14 April 2008] Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007, June 2007. Accessed at www.cdc.gov/ncidod/dhqp/pdf/guidelines/Isolation2007.pdf
17. U.S. Preventive Services Task Force. Screening for hepatitis C virus infection: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2004; 140:465–479. [PMID: 15023713]. [PubMed: 15023713]
18. Alter MJ, Seeff LB, Bacon BR, Thomas DL, Rigsby MO, Di Bisceglie AM. Testing for hepatitis C virus infection should be routine for persons at increased risk for infection. *Ann Intern Med.* 2004; 141:715–717. [PMID: 15520428]. [PubMed: 15520428]

19. Vrielink H, Reesink HW, van den Burg PJ, et al. Performance of three generations of anti-hepatitis C virus enzyme-linked immunosorbent assays in donors and patients. *Transfusion*. 1997; 37:845–849. [PMID: 9280331]. [PubMed: 9280331]
20. Alberti A. Towards more individualised management of hepatitis C virus patients with initially or persistently normal alanineamino-transferase levels. *J Hepatol*. 2005; 42:266. [PMID: 15664254]. [PubMed: 15664254]
21. Cacoub P, Renou C, Rosenthal E, et al. Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Medecine Interne et Maladies Infectieuses sur le Virus de l'Hepatite C. *Medicine (Baltimore)*. 2000; 79:47–56. [PMID: 10670409]. [PubMed: 10670409]
22. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 1998; 47:1–39. [PMID: 9790221].
23. Simmonds P. Viral heterogeneity of the hepatitis C virus. *J Hepatol*. 1999; 31(Suppl 1):54–60. [PMID: 10622561]. [PubMed: 10622561]
24. Marcellin P. Hepatitis C: the clinical spectrum of the disease. *J Hepatol*. 1999; 31(Suppl 1):9–16. [PMID: 10622554]. [PubMed: 10622554]
25. Wiley TE, McCarthy M, Breidi L, et al. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology*. 1998; 28:805–809. [PMID: 9731576]. [PubMed: 9731576]
26. Benson GD, Koff RS, Tolman KG. The therapeutic use of acetaminophen in patients with liver disease. *Am J Ther*. 2005; 12:133–141. [PMID: 15767831]. [PubMed: 15767831]
27. Rambaldi A, Jacobs BP, Iaquinto G, et al. Milk thistle for alcoholic and/or hepatitis B or C liver diseases—a systematic cochrane hepato-biliary group review with meta-analyses of randomized clinical trials. *Am J Gastroenterol*. 2005; 100:2583–2591. [PMID: 16279916]. [PubMed: 16279916]
28. Verma S, Thuluvath PJ. Complementary and alternative medicine in hepatology: review of the evidence of efficacy. *Clin Gastroenterol Hepatol*. 2007; 5:408–416. [PMID: 17222587]. [PubMed: 17222587]
29. Singal AK, Anand BS. Mechanisms of synergy between alcohol and hepatitis C virus. *J Clin Gastroenterol*. 2007; 41:761–772. [PMID: 17700425]. [PubMed: 17700425]
30. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis*. 2001; 32:492–497. [PMID: 11170959]. [PubMed: 11170959]
31. ANRS HCO2 RIBAVIC Study Team. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA*. 2004; 292:2839–2848. [PMID: 15598915]. [PubMed: 15598915]
32. Kim AI, Dorn A, Bouajram R, et al. The treatment of chronic hepatitis C in HIV-infected patients: a meta-analysis. *HIV Med*. 2007; 8:312–321. [PMID: 17561878]. [PubMed: 17561878]
33. Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med*. 2001; 345:41–52. [PMID: 11439948]. [PubMed: 11439948]
34. PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*. 2004; 140:346–355. [PMID: 14996676]. [PubMed: 14996676]
35. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002; 347:975–982. [PMID: 12324553]. [PubMed: 12324553]
36. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*. 2001; 358:958–965. [PMID: 11583749]. [PubMed: 11583749]
37. Virahep-C Study Group. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology*. 2006; 131:470–477. [PMID: 16890601]. [PubMed: 16890601]

38. Jakiche R, Borrego ME, Raisch DW, et al. The cost-effectiveness of two strategies for vaccinating US veterans with hepatitis C virus infection against hepatitis A and hepatitis B viruses. *Am J Med Sci.* 2007; 333:26–34. [PMID: 17220691]. [PubMed: 17220691]
39. Immunization of health-care workers: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep.* 1997; 46:1–42. [PMID: 9427216].
40. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 1997; 46:1–24. [PMID: 9132580].
41. Kelleher TB, Afdhal N. Maintenance therapy for chronic hepatitis C. *Curr Gastroenterol Rep.* 2005; 7:50–53. [PMID: 15701299]. [PubMed: 15701299]
42. Forestier N, Reesink HW, Weegink CJ, et al. Antiviral activity of telaprevir (VX-950) and peginterferon alfa-2a in patients with hepatitis C. *Hepatology.* 2007; 46:640–648. [PMID: 17879366]. [PubMed: 17879366]
43. Soza A, Everhart JE, Ghany MG, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. *Hepatology.* 2002; 36:1273–1279. [PMID: 12395340]. [PubMed: 12395340]
44. PROACTIVE Study Group. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatology.* 2004; 40:1450–1458. [PMID: 15565613]. [PubMed: 15565613]
45. U.S. Food and Drug Administration. [on 14 April 2008] FDA Public Health Advisory: Erythropoiesis-Stimulating Agents (ESAs). Accessed at www.fda.gov/cder/drug/advisory/RHE2007.htm
46. TPL102357 Study Group. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. *N Engl J Med.* 2007; 357:2227–2236. [PMID: 18046027]. [PubMed: 18046027]
47. Davis GL, Wong JB, McHutchison JG, et al. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology.* 2003; 38:645–652. [PMID: 12939591]. [PubMed: 12939591]
48. Poordad F, Reddy KR, Martin P. Rapid virologic response: a new milestone in the management of chronic hepatitis C. *Clin Infect Dis.* 2008; 46:78–84. [PMID: 18171217]. [PubMed: 18171217]
49. Dienstag JL, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. *Gastroenterology.* 2006; 130:231–264. quiz 214–7. [PMID: 16401486]. [PubMed: 16401486]
50. AASLD. AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology.* 2005; 41:1407–1432. [PMID: 15880505]. [PubMed: 15880505]
51. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol.* 2004; 130:417–422. [PMID: 15042359]. [PubMed: 15042359]
52. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology.* 2005; 42:1208–1236. [PMID: 16250051]. [PubMed: 16250051]
53. American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. *Hepatology.* 2004; 39:1147–1171. [PMID: 15057920]. [PubMed: 15057920]
54. U.S. Department of Veterans Affairs. [on 14 April 2008] The United States Department for Veterans Affairs Hepatitis C Testing and Prevention Counseling Guidelines for VA Health Care Practitioners. Accessed at www.hepatitis.va.gov

CME Questions

1. An 84-year-old man comes for a follow-up visit after being diagnosed with hepatitis C. Liver chemistry tests are abnormal, and serum HCV RNA is positive. Medical history is significant for ischemic cardiomyopathy with an ejection fraction of 15%. The patient had a blood

transfusion 20 years ago at the time of coronary artery bypass graft surgery. He has no history of excessive alcohol intake.

On physical examination, he appears chronically ill. Pulse rate is 80/min, and blood pressure is 90/60 mm Hg. There are no stigmata of chronic liver disease. Jugular venous distention is present. Bibasilar crackles and a prominent S3 are auscultated. The liver is pulsatile and slightly enlarged. There is no ascites, but mild pedal edema is noted. Complete blood count is normal, serum aspartate aminotransferase level is 73 U/L, serum alanine aminotransferase level is 84 U/L, serum alkaline phosphatase level is 132 U/L, and serum total bilirubin level is 1.0 mg/dL (17.1 μ mol/L). Abdominal ultrasonography shows mild hepatomegaly, a normal-sized spleen, and no ascites.

Which of the following is most appropriate for managing this patient's hepatitis C at this time?

- A. Liver biopsy
- B. Hepatitis C virus genotyping
- C. Pegylated interferon
- D. Pegylated interferon and ribavirin
- E. No further testing or treatment

2. A 38-year-old man with HIV infection and hepatitis C is evaluated after moving to a new city. HIV infection and hepatitis C were diagnosed 1 year ago, at which time his CD4 cell count was 523/ μ L (0.523×10^9 /L), and his plasma HIV RNA viral load was 8522 copies/mL. The patient has remained asymptomatic, and his previous physician did not recommend antiretroviral therapy.

On physical examination at today's visit, he appears well. His liver is not enlarged, his spleen is not palpable, and there are no signs of liver disease. The remainder of the examination is normal. His CD4 cell count is 449/ μ L (0.449×10^9 /L); plasma HIV RNA viral load is 12 220 copies/mL; and his liver chemistry studies, serum albumin level, and prothrombin time are all normal.

Which of the following is the most appropriate management of this patient's hepatitis C at this time?

- A. Qualitative hepatitis C virus RNA viral load testing
- B. Liver biopsy
- C. Pegylated interferon
- D. Pegylated interferon and ribavirin

3. A 55-year-old man who recently emigrated from Southeast China to the United States is evaluated for a 3-month history of right upper-quadrant

pain and a 23-kg (50-lb) weight loss from baseline. He has noticed that his eyes have become yellow and his skin darker over the past 6 weeks. Although he is anorexic, he has had no midepigastria pain, dyspepsia, nausea, or vomiting.

On physical examination, he is cachectic and jaundiced. The abdomen is distended, with shifting dullness to percussion. The liver is palpable approximately 10-cm below the right costal margin. A computed tomographic scan of the abdomen reveals a large, space-occupying hepatic mass, which is confirmed as hepatocellular carcinoma on biopsy.

Which of the following infectious pathogens is the most likely cause of this patient's disease?

- A. Hepatitis B or C virus
- B. Epstein-Barr virus
- C. Human papillomavirus
- D. *Helicobacter pylori*

4. A 65-year-old man is evaluated for left upper-quadrant abdominal discomfort, early satiety, and recent weight loss (5% loss of baseline weight in 6 months). On physical examination, lymphadenopathy is absent, but the spleen is palpable to the level of the umbilicus. The remainder of the physical examination and the history are noncontributory.

The leukocyte count is 18,000/ μ L (18×10^9 /L), with 60% lymphocytes.

Splenomegaly and multiple lymph nodes smaller than 1 cm are visible in the mesenteric and retroperitoneal lymph node regions by computed tomographic scans of the chest, abdomen, and pelvis. A marginal-zone B-cell lymphoma—an indolent, low-grade lymphoma—is identified by flow cytometry.

Identification of which of the following infectious pathogens would be most helpful in the management of this patient?

- A. Hepatitis C virus
- B. Epstein-Barr virus
- C. Human T-cell leukemia virus 1
- D. *Helicobacter pylori*
- E. Hepatitis B virus

5. A 44-year-old man was recently found to have abnormal serologic test results for viral hepatitis when he attempted to donate blood. The patient is asymptomatic. He used injection drugs and drank alcohol excessively for 2 years 25 years ago but has not used either drugs or alcohol since. Medical history is otherwise unremarkable, and he takes no medications.

Physical examination discloses a body mass index of 23, no stigmata of chronic liver disease, and a normal-sized liver. Serum aspartate aminotransferase level is 53 U/L, serum alanine aminotransferase level is 64 U/L, serum alkaline phosphatase level is 89 U/L, and serum total bilirubin level is 0.9 mg/dL (15.39 μ mol/L). The patient is negative for hepatitis B surface antigen, positive for antibody to hepatitis B surface antigen, positive for IgG antibody to hepatitis B core antigen, negative for IgM antibody to hepatitis B core antigen, and positive for antibody to hepatitis C virus. Abdominal ultrasonography is normal.

Which of the following diagnostic studies should be done next?

- A. Hepatitis B e antigen (HBeAg)
- B. Hepatitis B virus DNA (HBV DNA)
- C. Hepatitis C virus RNA (HCV RNA)
- D. IgM antibody to hepatitis A virus (IgM anti-HAV)

in the clinic Tool Kit Hepatitis C Infection

PIER Module pier.acponline.org/physicians/diseases/d163/d163.html

Access the PIER module on hepatitis C

Patient Information www.annals.org/intheclinic/tools

Download copies of the Patient Information sheet that appears on the following page for duplication and distribution to your patients.

Centers for Disease Control and Prevention www.cdc.gov

Patient handouts on HCV infection in English and other languages

National Institute for Diabetes and Digestive Diseases and Kidney Diseases of the National Institutes of Health (NIDDK) digestive.niddk.nih.gov

Information for patients entitled “What I need to know about Hepatitis C.”

American Liver Foundation www.liverfoundation.org/

Patient information in question and answer format.

U.S. Veterans Affairs National Hepatitis C Program www.hepatitis.va.gov/

Information about hepatitis C for patients and the public.

MELD Calculator www.unos.org/resources/MeldPeldCalculator.asp?index-98

MELD Calculator for adult and pediatric patients.

What you should know about Hepatitis C

What is Hepatitis C?

- Hepatitis C virus can cause liver disease.
- People can get hepatitis C virus if they share or have ever shared needles or have other contact with blood from someone with hepatitis C. People can also get hepatitis C if they have sex with many people.
- Most people don't know they have hepatitis C virus until they have blood tests that show it.
- If you have hepatitis C, you may get a liver biopsy. Biopsy takes a small piece of the liver to look at under a microscope to find out how bad the liver disease is.

Treatment

- There are medicines that can help hepatitis C disease. Ask your doctor whether these medicines might be right for you.
- Sometimes people with hepatitis C need to take medicines for many months.
- Be sure to take the medicines the way your doctor tells you and report any side effects.
- The medicines can cure hepatitis in some people but not in everyone.
- If you have hepatitis C, do not drink alcohol and check with your doctor before taking any drugs because some might hurt the liver.

Other Problems from Hepatitis C

- A few people who have hepatitis C for a long time can get scarring in the liver (cirrhosis) or liver cancer.
- People with cirrhosis need to see their doctor often to check for liver cancer.
- Sometimes people with cirrhosis or liver cancer have surgery to get a new liver (liver transplantation).

Table 1**Laboratory Tests and Other Studies for Hepatitis C***

Test	Notes
HCV Ab ELISA (first-line assay)	Sensitivity and specificity of 93% to 99%; positive results do not distinguish between acute, chronic, or resolved infection; may be falsely negative in immunosuppressed patients or patients on hemodialysis
HCV RNA	Use to assess for chronic HCV infection if the HCV Ab ELISA is positive; positive result is associated with chronic infection
ALT and AST levels	ALT levels are the most common abnormality in HCV infection; usually <10 times the upper reference level; underestimates infection and lacks specificity for HCV
Other liver function tests	Prothrombin time and levels of total bilirubin, total protein, albumin, and alkaline phosphatase are usually normal until end-stage liver disease is present
CBC with platelet counts	Low platelets can suggest the presence of cirrhosis; low sensitivity
Serum ferritin level	Elevated levels of ferritin are found in many patients with chronic hepatitis C
ANA and anti-smooth muscle antibodies	Antibody testing has low sensitivity and specificity; low levels are often present in chronic hepatitis C but have no clinical relevance
HIV antibody by ELISA	Risk factors for HIV and HCV are similar; all patients with HCV infection should be screened for HIV infection
HBV serologies	All patients with HCV infection should be screened for HBV infection
HCV genotyping	Only assess when HCV RNA is present; high sensitivity and specificity; useful in determining treatment-response rates and duration of treatment
Imaging studies (ultrasonography, CT, or MRI of the liver)	Usually reserved for the patients with a likely diagnosis of cirrhosis
Special tests (cryoglobulin level, urinary porphyrin level)	Testing for cryoglobulins is appropriate in patients with evidence of vasculitis or glomerulonephritis; testing for urinary porphyrins is appropriate when porphyria cutanea tarda is suspected

* ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate aminotransferase; CBC = complete blood count; CT = computed tomography; MRI = magnetic resonance imaging; ELISA = enzyme-linked immunosorbent assay; Ab = antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RNA = ribonucleic acid.

Table 2**Differential Diagnosis of Hepatitis C ***

Disease	Characteristics	Laboratory Work-Up
Chronic hepatitis B and D	Epidemiologic features resemble those of chronic hepatitis C	Test for HBsAg and anti-HBc; if positive, testing for anti-HDV is appropriate
Autoimmune hepatitis	Largely affects women, other autoimmune disorders may be present, including autoimmune thyroiditis; Sjogren syndrome; and celiac sprue	Test for ANA and serum immunoglobulin levels
Drug-induced chronic hepatitis	History of drug use and improvement on discontinuation of drug	Liver biopsy sometimes used in diagnosis but usually not needed, as discontinuation of the offending agent is necessary in management
Metabolic and genetic disorders (e.g., hemochromatosis, Wilson disease, α 1-antitrypsin deficiency)	Iron overload is not usually clinically evident until mid-life; Wilson disease is rarely diagnosed after age 40	Testing for iron overload (serum iron level, transferrin saturation, genetic testing, and if necessary, hepatic iron index based on quantitative measurement of iron in liver biopsy sample); testing for Wilson disease (serum ceruloplasmin level, serum and urinary copper levels in patients <40 years, and if necessary, measurement of hepatic copper concentration in liver biopsy sample); test for α 1-antitrypsin deficiency (serum level and phenotype); obtain stain of liver biopsy tissue, if available, for PAS-positive diastase-resistant globules
Alcoholic hepatitis	AST level exceeds ALT level in 90% of cases; history of excessive alcohol consumption and improvement on discontinuation	Liver biopsy demonstrates histologic features of alcoholic hepatitis although liver biopsy often not necessary for diagnosis
Nonalcoholic steatohepatitis	Associated with diabetes mellitus, obesity, and other disorders; requires the absence of history of alcohol consumption	Steatohepatitis is confirmed by liver biopsy

* ALT = alanine aminotransferase; ANA = antinuclear antibody; anti-HBc = anti-hepatitis B core antigen; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen; HDV = hepatitis D virus; PAS = periodic acid-Schiff.

Table 3

Drug Treatment for Hepatitis C with Pegylated Interferon Regimens*

Agent	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Pegylated interferon- α -2a, and α -2b monotherapy	Antiviral, immunomodulatory	For interferon- α -2a, 180 μ g sc weekly. For interferon α -2b, 1.0 μ g/kg sc weekly	Sustained virologic response rate of 25% to 39%	Flulike illness, fatigue, depression or severe mental illness, cytopenias, rashes, and thyroid dysfunction; teratogen	Contraindicated in the presence of severe depression, cytopenias, or pregnancy
Pegylated interferon- α -2a plus ribavirin	Antiviral, immunomodulatory	For interferon- α -2a, 180 μ g sc weekly, plus ribavirin, 800 mg daily for genotypes 2 and 3 1000 to 1200 mg daily for genotype 1 depending on weight [†]	Sustained virologic response rate of 54%; genotype 1, 42%; genotypes 2 or 3, 82%	As above with pegylated interferon- α monotherapy plus hemolytic anemia	Contraindicated as with pegylated interferon- α -2a and 2b (see above) and in the presence of renal failure, anemia, and significant or unstable CAD
Pegylated interferon- α -2b plus ribavirin	Antiviral, immunomodulatory	For interferon- α -2b, 1.5 μ g/kg sc weekly plus ribavirin 800 mg po daily for genotypes 2 and 3 and 800 to 1400 mg daily for genotype 1, depending on weight [†]	Sustained virologic response rate of 42%; genotypes 2 and 3, 82%	As above with pegylated interferon- α monotherapy plus hemolytic anemia	Contraindicated as with pegylated interferon- α -2a and 2b (see above) and in the presence of renal failure, anemia, and significant or unstable CAD

* CAD = coronary artery disease; HCV = hepatitis C virus; po = oral; RNA = ribonucleic acid; sc = subcutaneous.

[†] Duration of therapy is typically 12 months. Six months is adequate for genotypes 2 and 3, but cirrhotic patients are often treated for 12 months. Testing for HCV RNA after 12 weeks of treatment is useful in deciding whether to continue therapy (if HCV RNA is negative or there is a >2-log decrease in viral load) for an additional 9 months in genotype 1.

Table 4

Side Effects of Drugs Used in the Treatment of Hepatitis C

Common Interferon-α Side Effects
Fatigue
Flulike symptoms
Nausea and vomiting
Headaches
Low-grade fever
Weight loss
Irritability
Depression
Hair thinning
Bone marrow suppression
Irritation at the injection site
Common Ribavirin Side Effects
Hemolytic anemia
Fatigue
Pruritus
Rashes
Cough, bronchospasm, dyspnea
Uncommon Interferon-α Monotherapy and Combination Therapy Side Effects
Autoimmune thyroiditis
Seizures
Suicidal ideation or attempts
Retinopathy
Sepsis
Myocardial infarction
Pulmonary fibrosis