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Clinical Monitoring of Chronic Hepatitis C Based on its Natural History and Therapy

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Abstract

Hepatitis C virus (HCV) infection is a major public health problem and a leading cause of chronic liver disease. Chronic HCV infection often follows a progressive course over years and can result in cirrhosis, hepatocellular carcinoma, and need for liver transplantation. In the United States alone, the estimated prevalence of HCV infection is up to 5.1 million persons. The optimal approach to detecting HCV infection is to screen persons for possible history of risks of exposure to virus and to test those selected individuals with risk factors. Both host and viral factors may be important contributors to the natural history of HCV. Currently, effective pharmacologic therapy are available to induce sustained virologic response (SVR) or virologic "cure," which results in improved morbidity and mortality. Patient education before treatment is essential and should include a full discussion of potential side effects. It is important to work collaboratively and closely with patients to ensure early recognition of adverse events and to effectively manage them in order to ensure treatment compliance. This paper provides a thorough overview on screening for the diagnosis, clinical management, and treatment indications and contraindications for chronic hepatitis C.

Keywords

Hepatitis C virus (HCV); *chronic hepatitis C (CHC)*; *hepatitis C treatment*; *cirrhosis*; *chronic liver disease*

INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease. The World Health Organization (WHO) estimates that up to 180 million people are infected with HCV worldwide (WHO Website). From the National Health and Nutrition Examination Surveys (NHANES), the prevalence of HCV in the US between 1999 and 2002 was 1.6%, which is 4.1 million persons positive for antibody to Hepatitis C[1], but recent studies showed that the current prevalence may be as high as 5.1 million persons.[2] Chronic HCV (CHC) infection can be complicated by cirrhosis and hepatocellular carcinoma (HCC). In the US, HCV-related disease is the leading cause of death from liver disease and is a major indication for liver transplantation.[3]

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MOLECULAR BIOLOGY OF HEPATITIS C VIRUS (HCV)

In the 1970s, it became apparent that a large population with acute and chronic hepatitis could not be explained by hepatitis A or B viral infection. It was not until 1989 that the HCV was cloned. The HCV genome is a positive-strand RNA molecule of 9,500 nucleotides, which encodes a large polyprotein of about 3,000 amino acids.[4] This large protein undergoes post-translational processing by host and viral enzymes to form structural and nonstructural proteins and enzymes of the virus. The 5' terminus of the viral RNA is highly conserved, which serves as useful target for amplication in diagnostic assays.

The polymerase enzyme of RNA viruses lack proofreading ability and therefore are unable to correct errors during replication. These nucleotide changes result in tremendous viral heterogeneity. This heterogeneity is important in the diagnosis of infection, pathogenesis of disease, response to treatment, and prevents the development of an effective vaccine.[5] Six major genotypes and more than 50 subtypes of HCV have been defined.[6] The evolution of various genotypes is influenced by infection patterns, population migration, immune selection, and replication efficiency.[7,8]

HEPATITIS C SCREENING AND COUNSELING

The optimal approach to detecting HCV infection is to screen persons for possible history of risks of exposure to this virus and to test those selected individuals with risk factors. Table 1 summarizes people who should be tested for Hepatitis C. Intravenous drug use is the primary mode of HCV transmission in the United States. Therefore, individuals who have ever used illicit injections (even if only once) and those intranasal drug users who share paraphernalia should be tested for HCV infection.[1,9,10] Individuals who have received blood transfusions or organ transplant before 1992 should also be tested.[11] After the introduction of highly sensitive tests to screen blood donors for HCV, transfusion-related transmission of HCV has become very rare.[9,12] Additionally, patients with unexplained elevations in aminotransferase levels, hemophilia patients who received blood products before 1987 (after 1987 viral inactivation procedures were implemented), hemodialysis patients, children born to HCV-infected mothers, or patients with human immunodeficiency virus (HIV) infection should be screened for HCV infection.

Folk medicine practices (including acupuncture), body piercing, tattooing, and commercial barbering are potential modalities for HCV transmission when appropriate infection control are not implemented.[11]

NATURAL HISTORY OF CHRONIC HEPATITIS C INFECTION

HCV causes approximately 20% of acute hepatitis in the United States.[13] The risk of chronic infection after an acute episode of hepatitis C is high, with studies showing between 80 to 100% remaining HCV RNA positive and 60 to 80% having persistent elevation in liver enzymes.[14] Many host factors may be involved in the ability of the host to spontaneously clear the virus. These factors include host's age, gender, and other comorbid conditions, such body weight, hepatic steatosis, excessive alcohol assumption, and co-infection with hepatitis B virus (HBV) and/or HIV.

The natural history of CHC has been difficult to fully define because of the long course of the disease. A systematic review of 111 studies showed that the estimated prevalence of cirrhosis was approximately 16% (95% CI 14–90%) after 20 years of HCV infection.[15] In one case series of US patients with chronic post-transfusion CHC who were followed for a mean of 22 years after transfusion, 51% had cirrhosis, 23% had active chronic hepatitis, and 5% had HCC. The mean duration of infection among patients with cirrhosis was 20.6 years.[16] Other studies from Japan and France demonstrated similar results.[17–19]

Cirrhosis can result in major complications of liver failure in patients with chronic HCV infection. However, not all patients with cirrhosis will develop complications. In a study of 384 HCV patients with compensated cirrhosis, it was demonstrated that the risk of developing hepatic decompensation was 3.9% per year.[20] In another report of 200 patients with previously compensated cirrhosis, the most common forms of decompensation over the mean follow-up of 34 months were ascites (48.0%), gastrointestinal bleeding (32.5%), severe bacterial infection (14.5%), and encephalopathy (5%).[21] The probability of survival after initial decompensation were 81.8% and 50.8% at 1 and 5 years, respectively.

FACTORS PREDICTIVE OF DISEASE PROGRESSION

Both host and viral factors may be important contributors to the natural history of HCV. Male gender,[22] acquisition of the HCV at an older age,[18] and higher body mass index[23,24] are associated with faster progression of liver disease. Alcohol intake has been shown to promote the progression of HCV, even in patients with relatively low alcohol intake.[18,25,26] The daily use of marijuana is a risk factor for progression of fibrosis in patients with HCV, which is thought to be through stimulation of endogenous hepatic cannabanoid receptors.[27]

The host cellular immune system to HCV may also play a role in severity of liver injury. In a retrospective study of 355 patients with chronic HCV, African-Americans have a slower rate of progression of liver disease compared to non-African-Americans. The authors suggest the slower rate of progression of liver fibrosis in African-Americans may reflect less immunological recognition of HCV-infected liver cells.[28] Asti et al demonstrated that there was a correlation between severity of liver disease with human leukocyte antigen (HLA) genes.[29] Low frequency of alleles TNFB*1, DRB1*1104, and DRB3*03 appears to have a protective role, while DRB1*1001 appears to be associated with increasing disease severity. The activity of transforming growth factor B1 (TGF B1) and angiotensin II have been shown to have a significant relationship with the development of liver fibrosis, suggesting that genetic polymorphism of these genes may contribute to fibrosis progression rate.[30]

Though IL28B genotype is a known predictor of spontaneous clearance of HCV infection and patient's response to treatment with peginterferon and ribaviran, its effect on progression of fibrosis is unclear. Marabita et al demontrated that IL28B was not associated with fibrosis progression or risk of developing advanced liver disease.[22] A subsequent study by Bochud et al was not predictive of progression of fibrosis among patients with genotype 1, but may have a role in non-genotype 1 infection.[31]

The effect of viral factors on disease progression remains unclear. Viral inoculum does not appear to be important.[32] Data on viral genotype and disease progression appears to be

contradictory. Several cross-sectional studies shown that genotype 1b is overrepresented among patients with cirrhosis and HCC,[33,34] but subsequent studies have failed to show this association after adjusting for various patient factors.[35,36] However, patients with co-infection with more than one HCV genotypes appear to have an accelerated disease course, suggesting a synergistic harmful effect.[35,36] Co-infection with Hepatitis B[37,38] and HIV[39,40] also predicts more rapid disease progression than infection with HCV alone.

The best clinical predictor of disease progression appears to be amount of inflammation and fibrosis in liver biopsy. Yano et al demonstrated with mild inflammation (portal inflammation alone) and no fibrosis had only 1.2% per year risk of progression to cirrhosis. Among patients with moderate chronic hepatitis (periportal inflammation greater than 30% of limiting plate), there was a 4.6% per year risk of progression to cirrhosis. In contrast, patients with bridging fibrosis and severe inflammation all developed cirrhosis within 10 years.[41]

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial of 1050 patients defined clinical outcomes as increased in Childs-Pugh score to seven or greater, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and liver-related death. The multivariate analysis showed that factors predictive of these clinical outcomes were elevated AST/ALT ratio, elevated total bilirubin, low albumin, low platelet, and increasing Ishak fibrosis score. Additionally, clinical factors predictive of histologic progression on liver biopsy were body mass index, degree of steatosis, and low platelet count.[42]

CLINICAL EVALUATION AND LABORATORY TESTING FOR CHRONIC HEPATITIS C

History, Physical Exam, and Imaging—The process of diagnosing hepatitis C includes taking comprehensive medical history and physical examination.[43] A complete history should include evaluation of risk factors for chronic liver disease including a history of hepatitis, alcohol consumption, diabetes mellitus, use of illicit drugs, transfusions, family history of liver disease and cancer, travel, and the presence of autoimmune diseases. A full review of systems should include questions relating to fatigue, easy bruisability, lower extremity edema, weight loss, pruritus, increasing abdominal girth, and confusion or sleep disturbance (indicating encephalopathy). Physical examination can be focused on findings of chronic liver disease, including spider angiomata, palmar erythema, nail changes, digital clubbing, Dupuytren's contracture, gynecomastia, testicular atrophy, caput meduasae, ascites, hepatomegaly, splenomegaply, jaundice, and asterixis. Although radiographic findings can occasionally suggest the presence of cirrhosis, currently available imaging modalities are not sensitive or specific for use as a primary diagnostic modality.

Routine imaging may not be needed for initial diagnosis of CHC. However, when indicted, imaging may be useful to detect hepatomegaly and hepatic steatosis, splenomegaly, and the complications of cirrhosis such as ascites, hepatocellular carcinoma, and hepatic or portal vein thrombosis.

Laboratory Testing for HCV Infection—Two classes of assays are used in the diagnosis and management of HCV infection-serologic assay that detect antibody to HCV (anti-HCV) and molecular assays to detect viral nucleic acids. Anti-HCV can be used to detect HCV-specific antibody in the serum using different immunoassays. Two different enzyme immunoassays are approved for clinical use by the United States Food and Drug Administration. The specificity of the current enzyme immunoassays (EIA) is greater than 99%.[44] The recombinant immunoblot assay (RIBA) was originally developed as a more specific, supplemental assay to confirm the result of EIA testing.[45,46] However, the third generation EIA results are highly specific and the role of RIBA testing is rarely used.[47]

False negative results may occur in severe immunosuppression such as hypogammaglobulinemia, patients on hemodialysis, solid organ transplant recipients, and co-infection with HIV.[48–50] In 1997, the WHO established the international standard for HCV RNA nucleic acid technology and reported as the IU rather than viral copies.[51] All currently available assays have excellent specificity, in the range of 98% to 99%.[11]

The Center for Disease Control and Prevention (CDC) provides guidance to the use of HCV antibody and RNA testing.[46] No further testing is necessary if the EIA test is negative. If the EIA is positive, a confirmatory test using a high sensitive HCV RNA is necessary (See Table 2).

Genotyping is useful in clinical management for predicting likelihood of response and determining optimal duration of therapy. Therefore, the HCV genotype needs to be defined in all infected people. In the United States, genotype 1 is most common, followed by genotypes 2 and 3.

Liver Biopsy and Noninvasive Tests to Assess Fibrosis—There is great clinical utility in performing liver biopsy in patients with chronic HCV: (1) provides information on current status of liver injury; (2) identifies features useful in decision on therapy; (3) reveals degree of fibrosis and cirrhosis that necessitates surveillance programs for HCC and variceal screening. A liver biopsy is used to assess for grade and stage of liver injury and provides other histologic features important in predicting disease progression.[52] Two common non-HCV features on liver biopsy that may predict disease progression and response treatment are steatosis[52,53] and excess hepatocellular iron.[54]

The liver biopsy does have several drawbacks including pain, bleeding, perforation of other organs, and is subjected to sampling error and requires high level of expertise to interpret accurately.[55] The decision to perform a liver biopsy should be based on whether treatment is considered, taking into account the duration of infection and other indices for advanced liver disease (ie, platelet count), viral genotype, and patient's motivation to be treated.

In the past decade, there has been the development of noninvasive testing to predict hepatic fibrosis based on direct and indirect serum markers (ie, FibroSURE™) as well as imaging modalities to measure liver stiffness (ie, FibroScan®).[56] Fibrosure combines combines α2-macroglobulin, haptoglobin, γ-glutamyl transpeptidatse, apolipoprotein A1, alanine transaminase, and total bilirubin into a proprieteary algorithm for fibrosis and inflammatory

activity.[57] Recent studies have demonstrated a potential utility for these noninvasive tests among chronic HCV with regards to stratifying patients with more moderate to severe stage disease.[58,59]

Indications for Chronic Hepatitis C Treatment

Before starting treatment—Patient education before treatment is essential and should include a full discussion of potential side effects. Factors that should be considered in determining whether HCV therapy should be considered includes—host factors (race, age, medical comorbidities, drug interactions, psychological factors, motivation, ability to adhere to treatment, and IL-28B genotype), stage of liver disease, and prior treatment history.[60] It is important to work collaboratively and closely with patients to ensure early recognition of adverse events and to effectively manage them in order to ensure treatment compliance. A comprehensive and multidisciplinary program is extremely helpful for patients undergoing treatment and has been shown to improve adherence to therapy and treatment success.[61]

Indications—All treatment-naïve patients with compensated liver disease who are willing to be treated and have no contraindications to pegylated-interferon (IFN) or ribavirin (RBV) should be considered for treatment (Table 3). The backbone for the treatment of genotype 1 remains with IFN and RBV. The addition of direct acting antiviral (DAA), including protease inhibitors and NS5B RNA polymerase inhibitor, have high clinical efficacy among the genotype 1 with high SVR rates for previous relapsers but for null responders SVR rate remains low.[62,63] Therefore, HCV retreatment with triple therapy is indicated for relapsers and may be worthwhile for selected partial responders. However, previous null responders with suboptimal SVR may be better off waiting for more effective HCV therapies, if no evidence of advanced CHC.[60,63]

Identifying patients at higher risk for developing progressive disease is sometimes difficult. The presence of bridging fibrosis (Metavir stage 3) is a strong predictor of future progression to cirrhosis and therefore is an indication for treatment.[64] Patients with genotypes 2 and 3 may be treated at any histologic stage because of high frequency of sustained virologic response.[11,65] Patients who achieved SVR had a significant reduction in liver-related morbidity and mortality[66] and achieving SVR may also reduce the risk for development of HCC.[67,68]

Regardless of liver histologic stage, patients with extrahepatic manifestations such as cryoglobulinemia, porphyria cutanea tarda, leuckocytoclastic vasculitis, necrolytic acral erythema, and glomerulonephritis should be considered for treatment.[11,69]

Contraindications—As with all decisions in medicine, a balance must be made with benefit and risk related to therapy. Peg-interferon and ribavirin are contraindicated in patients with pregnancy, severe depression, solid organ transplant recipients, autoimmune hepatitis (or autoimmune conditions), untreated thyroid disease, pregnancy, severe concurrent medical disease (hypertension, heart disease, poorly controlled diabetes), failure to apply contraceptive measures during treatment, and known hypersensitivity to drugs used to treat HCV[11,70–72] (Table 4). Peg-interferon is contraindicated in patients less than 2 years

old because it contains benzyl alcohol, which has been linked to neurologic complications in infants.[73]

For patients with HCV genotype 1 infection, DAAs are not approved as monotherapy given high resistant rates and therefore contraindications to IFN/RBV also apply. Telapravir and boceprevir, the first generation protease inhibitors, are highly dependent on CYP3A for clearance and is contraindicated when combined with drugs that strongly induce or inhibit CYP3A.[74,75] Additionally, less than 1% of patients will develop a serious skin reaction of Stevens-Johnson Syndrome or Drug Rash with Eosinophilia and Systemic Syndrome while on telaprevir and these patients should have the medication discontinued and referred for immediate medical attention.[75] Recently approved in the United States are simeprevir (second generation protease inhibitor) and sofosbuvir (NS5B RNA polymerase inhibitor), which have significant lower side effects, less drug-drug interactions, and shorter treatment course may offer more therapeutic benefits than the first generation protease inhibitors.[63,76,77] In particular, sofosbuvir is a HCV nucleotide analog NS5B polymerase inhibitor that has been recently approved for HCV treatment and re-treatment. Depending on HCV genotype, it will be combined with ribavirin or IFN/RBV.[78,79] Thus, all IFN/RBV contraindications will apply to the related regimens.

Patient's characteristics where therapy can be considered, but would need to be individualized includes—patients who failed prior treatment with either interferon with or without ribavirin; liver biopsy with no or mild fibrosis; acute hepatitis C, current users of illicit drugs or alcohol but willing to participate in substance abuse program; co-infection with HIV; under 18 years of age; chronic renal disease (including those on hemodialysis); decompensated cirrhosis; liver transplant recipients.[11,72] It must be emphasized that selection of patients are guidelines and not fixed rules and treatment decisions should be made on a case-by-case basis.

Other Considerations—(1) Patients preference, readiness, motivation, engagement, and support; (2) ongoing assessment is needed, especially for those with relative contraindication; (3) regular follow-up is needed even for those with absolute contraindication; and (4) continuous support and management of other comorbid conditions.

General Management Issues

In addition to pharmacologic therapy for HCV, all patients with chronic HCV need education and counseling on measures which may be helpful in reducing progression of liver fibrosis. There are several studies that have reported associations between excessive alcohol use and the progression of liver fibrosis, development of HCC, and poorer response to treatment.[18] For patients with heavy alcohol use, patients be treated for alcohol dependency prior to starting pharmacologic treatment.

Obesity and its associated nonalcoholic fatty liver disease may also play a role in liver disease progression in HCVI-infected patients as well as HCV treatment response. It is therefore important to counsel overweight patients (BMI > 25kg/m^2) to attempt to lose weight.[11] A single report has showed that superimposition of hepatitis A infection in patients with chronic liver disease was associated with fulminant hepatitis.[80] Therefore,

patients with chronic HCV infection who has no antibody to hepatitis A should be administered the hepatitis A vaccine.[81] Given overwhelming evidence that patients with co-infection with hepatitis B have poorer prognosis, patients who has no immunity to Hepatitis B should also be immunized against Hepatitis B.[82]

In one prospective study, up to 42 percent of patients with chronic HCV reported using at least one herbal product, with most common agent being silymarin (milk thistle).[83] There have been several herbal mixtures associated with severe hepatotoxicity, fulminant hepatitis, and death.[84] Therefore, it is important to remind patients with chronic HCV to seek medical advice before taking any herbal products.

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Table 1

Risk factors that should prompt HCV Screening.

Any history of intravenous illicit drugs in the recent and remote past
Conditions associated with high prevalence of HCV infection
a) HIV infection
b) Hemophiliacs who received blood products (clotting factor concentrates) prior to 1987
c) Hemodialysis patients
d) Unexplained abnormal aminotransferase levels
Prior recipients of transfusions or organ transplants prior to 1992
Children born to HCV-infected mothers
Health careworkers after a needle stick injury or mucosal exposure to HCV-infected blood
Sexual partners of HCV-infected persons

Table 2

Clinical interpretations of HCV laboratory tests.

Anti-HCV	HCV RNA	Interpretation
(+)	(+)	Acute or chronic HCV based on clinical presentation
(+)	(−)	Resolution of HCV
(−)	(+)	(1) Early HCV infection (2) Chronic HCV in setting of immunocompromised state (3) False positive HCV RNA testing
(−)	(−)	Absence of HCV infection

Table 3

Risk factors that should prompt HCV Screening.

Age 18 years and older, and
HCV RNA positive in serum, and
Liver biopsy showing chronic hepatitis with bridging fibrosis or higher, and
Compensated liver disease (total bilirubin <1.5g/dL, INR 1.5; albumin <3.5, platelet 75,000 mm), and
Accepatable hematological and biochemic indices (hemoglobin 13g/dL for men 12g/dL women; neturophil 1500/mm3, and creatinine <1.5mg/dL), and
Willing to adhere to treatment requirements
No evidence of decompensated liver disease (encephalopathy or ascites)

Table 4

Characteristics of persons for whom therapy is contraindicated.

Major uncontrolled depression
Solid organ transplant (renal, heart, lung)
Autoimmune hepatitis or other autoimmune condition, which can be exacerbated by peginterferon and ribavirin
Untreated thyroid disease
Pregnant or not willing to comply with adequate contraception
Severe medical diseases such as severe hypertension, heart failure, coronary artery disease, poorly controlled diabetes, chronic obstructive pulmonary disease
Age less than 2 years old
Hypersensitivity to drugs used to treat HCV