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NATURAL HISTORY OF HEPATITIS C

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Abstract

Hepatitis C infection is a common cause of cirrhosis and indication for liver transplantation in the United States. The incidence of chronic hepatitis C has been declining but rates of cirrhosis and hepatocellular carcinoma are projected to rise. The outcome of chronic hepatitis C is variable. It is estimated that 20–25% will develop cirrhosis over a 25–30 year period. The rate of disease progression is influenced by many host, viral and environmental factors. Unfortunately, few can be modified.

Keywords

Natural history; hepatitis C virus; chronic hepatitis C; fibrosis; cirrhosis; decompensated liver disease

Introduction

Hepatitis C virus infection is an important cause of cirrhosis and hepatocellular carcinoma worldwide (HCC).¹ It is also a common cause of chronic liver disease in the United States (U.S.) and the leading indication for liver transplantation in the adult U.S. population. The incidence of chronic hepatitis C is declining in the U.S. but rates of cirrhosis and hepatocellular carcinoma are expected to increase.² Recent data estimate that approximately 1% of the non-institutionalized U.S. population have chronic HCV infection, corresponding to 2.7 million persons.³ Hepatitis C virus (HCV) is primarily transmitted through parental exposure to blood and other bodily fluids. Following exposure, an acute hepatitis with jaundice occurs in about 20% of persons although fulminant hepatitis is rare, occurring in less than 1% of persons. In the majority of cases the acute infection goes unnoticed. Spontaneous resolution may occur in 15–45% of persons and usually occurs in the first 6 months of exposure. The remainder develop a chronic hepatitis that has an unpredictable course. Approximately 20–30% of persons with chronic hepatitis will progress to cirrhosis

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over a 25–30 year period. The natural history study of chronic hepatitis C is greatly influenced by host, viral and environmental factors most of which are not modifiable, Table 1.⁴ This article will review the natural history of chronic hepatitis C and discuss the factors that influence its outcome.

Acute hepatitis C

The incidence of acute hepatitis C had been declining in the U.S. but a marked increase in cases was noted between 2010–2013, from 850 in 2010 to 2,138 in 2013, representing a 152% increase in cases of acute hepatitis C. This sharp rise has been attributed to an increase in injection drug use among the suburban population in the Eastern and Midwestern states.

The most common symptoms of acute hepatitis C include jaundice, nausea, abdominal pain and flu-like symptoms. In most individuals, HCV RNA is usually detectable within two weeks and anti-HCV antibodies within 12 weeks of exposure to HCV. Serum alanine aminotransferase (ALT) levels usually rise within 8–10 weeks, with a peak ALT of 10–20 times the upper limit of normal. Serum HCV RNA levels may fluctuate widely during the acute phase and even become negative transiently, only to reappear again. This finding is only seen in the acute phase and may be a clinical clue to the diagnosis of acute HCV infection. Spontaneous resolution occurs in 15–25% of subjects and may be up to 45% in persons who present with jaundice, children, and young women. Higher rates of spontaneous clearance were also observed in persons with certain polymorphisms (the rs12979860-C,⁵ rs8099917-T⁶ and the ss469415590 TT⁷) near to the IL-28B gene (interferon lambda). HLA class II alleles may play a role in spontaneous clearance. Less genetic diversity of the viral E1 and E2 envelope genes was observed in subjects with spontaneous recovery compared to those who progressed to chronic infection.⁸

Natural History of Chronic Hepatitis C

Chronic hepatitis C is defined as persistence of HCV RNA in the blood for more than 6 months after the onset of acute infection. About 55–85% of patients with acute hepatitis C transition to chronic hepatitis C, Figure 1. Once the infection becomes chronic, spontaneous resolution is rare. Chronic hepatitis C can subsequently lead to progressive fibrosis and eventually cirrhosis, end stage liver disease and hepatocellular carcinoma, Figure 1.

It is estimated that 20–30% patients with chronic hepatitis C will progress to cirrhosis. However, this rate is highly variable and dependent on the methodology used to define the natural history of the disease, whether prospective, retrospective or retrospective-prospective study designs and the population studied. This was highlighted in an analysis of 57 studies undertaken to estimate progression to cirrhosis. Studies were broadly classified as those from tertiary care liver clinics, post-transfusion cohorts, blood donors and community-based cohorts. Estimates of progression to cirrhosis after 20 years of chronic hepatitis C varied widely from a high of 24% for post transfusion cohorts and 22% for tertiary care liver clinics, to a low of 7% for community based cohorts and 4% for blood donors.⁹ Selection bias, recall bias and short duration of follow-up probably account for differences in the

estimated rate. Community-based cohort studies are likely to provide the best evidence for estimating disease progression at a population level.

Monitoring progression of fibrosis is another way of estimating the outcome of chronic hepatitis C. Since progression of fibrosis is the precursor of cirrhosis, following its progression should reflect the course of the disease. Fibrosis stage was shown to be a good predictor of development cirrhosis and clinical outcomes, need for liver transplantation, and liver-related death, confirming the importance of fibrosis as a surrogate for outcome of chronic hepatitis C.^{10–12} Cross-sectional biopsy studies estimate a period of 30 years to develop cirrhosis. However, since fibrosis progression is unlikely to be linear, performing repeated liver biopsies in subjects should provide a more accurate determination of the rate of progression of fibrosis. Paired liver biopsy studies suggest a time to cirrhosis of 30 to 40 years.^{11, 13–15}

Natural History of Cirrhosis

The development of cirrhosis is an important milestone in the natural history of chronic hepatitis C. Once cirrhosis develops, patients are at risk for decompensation including the development of ascites, spontaneous bacterial peritonitis, variceal hemorrhage and hepatic encephalopathy. Occurrence of any of these events heralds an increased risk of death or need for liver transplantation. Information on the natural history of hepatitis C after development of cirrhosis has been mostly derived from studies conducted at tertiary referral centers, which may not be representative of all persons with chronic hepatitis C. With this caveat, survival of patients with cirrhosis in the short and medium term is quite good. Five-year survival ranges from 85–91% with a 10-year survival of 60–79%. The rate of clinical decompensation is approximately 2–5% per year and the development of HCC 1–4% per year.¹⁶

The HALT-C trial provided important data on the natural history of patients with advanced fibrosis and cirrhosis.¹⁷ The study treated prior interferon non-responders with 6 months of peginterferon and ribavirin. Failures to this intervention were then randomized to low dose peginterferon or observation for the next 3.5 years. After 4 years of follow-up, outcomes occurred at a similar rate between the treated group, 34.1% and the control group 33.8%. The most common clinical outcome was an increase of 2 or more points in the Child–Turcotte–Pugh score (documented on two consecutive visits), which occurred in 109 patients (10.4%). Ascites was the most common clinical decompensation event that occurred in 59 patients (5.6%). Hepatocellular carcinoma occurred in 29 patients (2.8%): 13 (2.1%) in the subjects without and 16 (3.7%) in those with cirrhosis. Fifty-three patients (5.0%) died, 31 in the treatment group (15 of liver-related causes) and 22 in the control group (12 of liver-related causes). At 3.8 years, the overall death rate was 6.6% among patients who received peginterferon and 4.6% among control patients.

Once decompensation develops, there is an increased risk of death or need for liver transplant. One study followed 200 patients with HCV-related cirrhosis without known HCC after hospitalization for their first hepatic decompensation.¹⁸ During a mean follow-up of approximately 3 years, HCC developed in 33 (16.5%) patients, and death occurred in 85

patients (42.5%). The probability of survival after diagnosis of decompensated cirrhosis was 82% and 51% at 1 and 5 years, respectively.¹⁸ Development of HE and/or ascites as the first hepatic decompensation event was associated with a lower survival rate.

Factors That Influence The Outcome Of Chronic Hepatitis C

Host factors

Age At Infection—Age plays a major role in the progression of fibrosis. Multiple studies have shown that older age at infection was associated with more rapid progression of fibrosis.^{19–22} In one study, nine host, viral and environmental factors were correlated with fibrosis progression among 2,235 untreated patients who underwent liver biopsy. Fibrosis progression per year was defined as the ratio between fibrosis stage in Metavir units and duration of infection in years. Older age at infection >40 years, was independently associated with a faster rate of fibrosis progression.¹⁹

The reasons for the age-related differences in fibrosis progression are not clear. Alteration in physiologic or immunologic status with increasing age may be important. For example a decline in liver volume and liver blood flow with aging or decreased immunologic response might contribute to fibrogenesis or fibrinolysis.^{16,23} Alternatively, older individuals may have a greater prevalence of or exposure to factors associated with fibrosis progression. Based on these data, persons older than 50 years should be monitored more closely for disease progression and considered for treatment earlier in the course of their infection.

Gender—Many studies have shown that females have a higher rate of spontaneous resolution of acute HCV infection.^{24–28} Among young women who acquired hepatitis C from receipt of contaminated Rh immune globulin, 45% cleared the infection spontaneously. Similarly, studies of acute hepatitis C among drug users have shown that spontaneous clearance was higher among women compared to men.^{29–32}

Gender also influences the outcome of chronic infection. Males have a higher risk of progression to advanced liver disease, cirrhosis and HCC when compared to females. Differences in sex hormones have been proposed to explain the gender differences in the progression of the disease. Higher serum testosterone levels were shown to be associated with greater severity of fibrosis. For each 1 ng/mL increase in total serum testosterone, there was a 25% increase in risk of advanced fibrosis.³³ In contrast, estrogen has been proposed to play a protective role in women.³⁴ In cross-sectional studies, post-menopausal women (with presumed reduced estrogen levels) had higher rates of fibrosis progression compared to pre-menopausal women and nulliparous women had higher rates of fibrosis progression compared to multiparous women.³⁵ *In-vitro* data suggest that estrogen can modify extracellular matrix production and attenuate hepatic stellate cell activation resulting in less collagen production.

Race—Chronic hepatitis C is approximately 3 times more common among non-Hispanic Blacks when compared to non-Hispanic Whites.³ The prevalence of hepatitis C was similar among Latinos and non-Hispanic Whites. African Americans were more likely to be infected with genotype 1,^{36–38} have lower baseline serum ALT levels,^{36–38} less piecemeal

necrosis,^{36–38} less fibrosis,^{36–38} but higher rates of HCC.³⁹ Latinos were reported to have more severe necroinflammatory activity compared to non-Hispanic Whites and a higher prevalence of cirrhosis and HCC compared to African-Americans and non-Hispanic Whites.^{40–42} A higher prevalence of the metabolic syndrome, insulin resistance, and hepatic steatosis as well as genetic differences among Hispanics are likely important contributing factors.⁴¹

African Americans and Latinos have lower response rates to interferon-based therapy compared to non-Hispanic whites.^{43–45} A lower prevalence of the favorable IL28b C allele amongst African Americans and Latinos compared to Caucasians and Asians partially accounts for the lower response rates.⁵ Differences in HLA class II alleles influencing host immune response to the virus may also contribute to the racial differences in viral clearance.^{46,47}

Obesity—Obesity, defined as a BMI greater than 30 kg/m² is an independent risk factor for fibrosis progression and development of cirrhosis. In one study, subjects undergoing liver biopsy were classified as rapid or non-rapid progressors based on a fibrosis progression rate of >0.2 fibrosis units/year. It was shown that BMI >25 was predictive of rapid fibrosis progression.⁴⁸ Steatohepatitis associated with obesity and increasing circulating insulin levels are thought to be contributing factors responsible for fibrosis progression in chronic hepatitis C irrespective of the genotype.⁴⁹ Obesity is also found to be a risk factor for nonresponse to antiviral therapy independent of steatosis, genotype and the presence of cirrhosis. Obese individuals have an 80% lower chance of a sustained response to interferon-based therapy compared with normal or overweight patients.⁵⁰

Steatosis—Hepatic steatosis is a common finding among the general population ranging from 10–24%. Using the presence of fat on ultrasound as a surrogate for steatosis, the prevalence of steatosis was 21% in the NHANES-3 study of the non-institutionalized U.S. population.⁵¹ The prevalence of steatosis is approximately 2–3 times more common in persons with chronic hepatitis C ranging from 42–70%.^{52–56} The etiology of steatosis in patients with hepatitis C is multifactorial resulting from metabolic derangements in the host due to obesity but also due to HCV infection itself. Hepatic steatosis has been suggested to promote the development of fibrosis and hasten progression to cirrhosis, increase the risk for HCC and lower the response to interferon-based therapy. Non-alcoholic steatohepatitis (NASH) represents a more advanced form of steatosis and has been associated with progressive liver disease and cirrhosis. Therefore, co-existent NASH and chronic hepatitis C may result in more rapid progression of liver disease. Given these adverse consequences of steatosis and NASH, patients with hepatitis C should try to maintain an ideal body weight.

Insulin Resistance/Diabetes—Diabetes mellitus is a common co-morbidity in subjects with chronic hepatitis C ranging from 24–62%.^{57,58} The development of insulin resistance (IR)/diabetes in patients with chronic hepatitis C is complex and appears to be related to presence of the metabolic syndrome as well as a result of the viral infection both of which may independently lead to the development of cirrhosis. Two meta-analyses have suggested a strong association between chronic hepatitis C and the development of insulin resistance.^{59,60} However, some studies have found no association between chronic hepatitis C and pre-

diabetes or diabetes. Rather an association was found with elevated ALT and gamma glutamyl transpeptidase levels suggesting that inflammation per se may lead to IR and diabetes.⁶¹ Interestingly, eradication of HCV has been associated with improvement and even reversal of insulin resistance^{62–64} and diabetes.⁶⁵

Insulin resistance and diabetes are associated with faster progression fibrosis, increased risk of cirrhosis and its complications including HCC and lower response to therapy in patients with chronic hepatitis C. In one study of patients with cirrhosis, the presence of diabetes was an independent risk factor for decompensation, liver transplantation, and death. A population-based study from Taiwan reported that new-onset diabetes was an independent predictor of cirrhosis and hepatic decompensation. These findings suggest but do not prove that better control of diabetes or insulin resistance could lead to better outcomes among patients with chronic hepatitis C including those with cirrhosis.

Genetics—Although several host, viral, and environmental factors have been linked with outcome of CHC, they do not completely explain the variable outcome of the disease. A strong host immune response against HCV favors viral clearance. Therefore, variability in genes involved in the immune response may contribute to viral clearance. In a landmark study, a genetic polymorphism near the IL28B gene, encoding interferon-lambda-3 (IFN-lambda-3), was shown to be strongly associated with response to treatment with interferon and spontaneous clearance of HCV.⁵ The C allele of rs 12979860 and G allele of rs8099917 were associated with an almost two-fold change in treatment-related clearance of HCV compared to the T allele at both loci.⁵ This observation was true for individuals of both European and African ancestry. In another study of 1,015 subjects with chronic infection and 347 who spontaneously cleared the infection, the minor allele (G) of the SNP at position rs8099917 was associated with a greater than 2-fold progression to chronic HCV infection.⁶⁶ The IL28B CC genotype was also shown to be associated with greater hepatic necroinflammation, higher ALT, and worse clinical outcomes in subjects with chronic hepatitis C.⁶⁷ Other genetic factors also play a role in outcome of HCV infection but are beyond the scope of this review.

ALT levels—In population studies, increasing ALT levels were shown to be associated with a progressive increase in death from all causes and in particular liver-related death.⁶⁸ Persistently normal ALT levels are found in approximately 20–30% of patients with chronic hepatitis.^{69,70} Subjects with persistently normal ALT levels are more likely to have mild liver fibrosis on liver biopsy. In a review of 23 studies with over 1,100 subjects, 80% of subjects with a normal ALT level had mild fibrosis whereas only 20% had advanced fibrosis.⁷¹ Additionally, subjects with normal ALT levels progress at a much slower rate when compared to those with elevated ALT levels.^{72–75}

In cross-sectional biopsy studies, serum ALT was not predictive of severity of fibrosis. However, in paired liver biopsies, elevated ALT levels were associated with progression of fibrosis.^{11–13,14} Serum ALT was not predictive of development of clinical outcomes, however the AST/ALT ratio was predictive.⁷⁶ Patients with elevated serum ALT levels are also found to have increased risk for hepatocellular carcinoma. In a large Taiwanese study, the cumulative risk for HCC was 1.7% for ALT levels < 15 U/L and increased to 4.2% levels

between 15–45 U/L and to 13.8% for ALT levels > 45 U/L.⁷⁷ Therefore, monitoring of ALT levels is useful in managing chronic hepatitis C.

Exercise—Weight loss and exercise are known to cause reduction in steatosis, obesity, diabetes and insulin resistance leading to improvement in serum ALT levels and fibrosis, despite the persistence of the HCV RNA. The potential benefits of exercise in patients with chronic hepatitis C were shown in a study of 16 obese patients with chronic hepatitis C. Dietary intervention and increased exercise were associated with reduction in BMI, improved insulin sensitivity and serum ALT and AST levels suggesting that dietary and exercise intervention may improve hepatic and metabolic status in obese insulin-resistant CHC.⁷⁸ The intensity and type of exercise may be important to derive the beneficial effects. High intensity aerobic exercise training was shown to improve hepatic enzymes and also psychological well-being in patients with chronic hepatitis C. Aerobic exercise has also been shown to improve psychological well-being and quality of life in overweight and obese patients with CHC.^{79,80} Therefore, recommending exercise should be an important component in the management of chronic hepatitis C.

Viral Factors

HCV RNA Level—Unlike HIV infection, there is little evidence to support the notion that HCV viral load affects outcome of chronic hepatitis C. The viral load observed among persons with chronic hepatitis C usually ranges from 10^4 to 10^8 copies/mL with an average HCV RNA level of approximately 10^6 copies/mL.⁸¹ HCV-RNA levels tend to remain relatively stable when serial determinations were made over time and rarely fluctuate above or below 1 log of the baseline. HCV viral load does not differ among viral genotypes.⁸² The majority of studies have shown no correlation between HCV RNA level and histological outcome.^{83–85} Therefore, there is no role for serially assessing viral load in a patient. Viral load is predictive of response to treatment with lower viral load being associated with higher response rates.

HCV Quasispecies/Genotype—The HCV polymerase lacks proof reading capacity, as a result many errors are introduced during replication. Consequently, the virus circulates as a viral swarm or quasispecies. Viral quasispecies were shown to affect spontaneous viral clearance.⁸ Lower genetic diversity of the envelope region was associated with a higher rate of spontaneous clearance.

Six major genotypes have been identified based on a sequence divergence of 30% among isolates. HCV genotypes have a geographical distribution with genotype 1 being the most common worldwide, accounting for 46% of all HCV cases, approximately one-third of which are in East Asia. Genotype 3 is the next most prevalent globally, 30%. Genotypes 2, 4, and 6 are responsible for a total 23% of all cases and the remaining cases are comprised of genotype 5.⁸⁶ The association between HCV genotype and disease progression is not very clear. A meta-analysis of 16 studies suggested that HCV genotype 3 was associated with accelerated fibrosis progression in single biopsy studies but not paired biopsy studies.⁸⁷ It is possible that steatosis associated with genotype 3, an independent predictor of fibrosis progression, might be the cause of the fibrosis progression rather than the HCV genotype 3

itself. The most important clinical utility of HCV genotype is as a predictor of response to therapy. The development of HCV regimens with pangenotypic activity may preclude the need for genotyping altogether.

Co-infection With HBV—Hepatitis C virus shares similar routes of transmission as HBV, so coinfection with these viruses is not uncommon. The prevalence of HBV/HCV coinfection is about 2–10% but there is significant geographical variation.^{88–95} Interestingly, most studies of HBV-HCV co-infected subjects show that usually only a single virus predominates though which one was unpredictable.^{96,97} Several studies have shown that co-infected patients are at substantially higher risk for cirrhosis, HCC and overall mortality compared to HCV monoinfected patients. In a large U.S. cohort study, a significantly increased risk of cirrhosis (~89% increase), HCC (~112% increase), and death (~62% increase) were seen in HBV/HCV coinfecting patients who were HBV DNA positive when compared to monoinfected patients whereas the absence of HBV replication was associated with a clinical course similar to that of HCV monoinfected patients.⁹⁸ Therefore, patients with HBV and HCV coinfection require close monitoring for the development of cirrhosis and may warrant more intensive HCC screening.

Co-infection with HIV—CV and HIV share similar routes of transmission. The overall burden of HIV/HCV coinfection is estimated at 4 to 5 million people worldwide.⁹⁹ The prevalence of HIV/HCV varies geographically and by the mode of transmission. The highest rates are seen in injection drug users and men who have sex with men. HCV infection is not associated with an increased rate of AIDS-defining events or deaths.¹⁰⁰ However, HIV has a number of adverse consequences on the outcome of HCV infection. HIV has been shown to increase the rate of chronic HCV infection,^{101,102} to increase HCV RNA levels^{81,101,103,104} and is associated with faster progression of fibrosis and development of cirrhosis. Response rates to interferon-based treatment are also lower among co-infected persons. Prior to HAART therapy, most co-infected individuals died from complications of HIV infection. However, in the post-HAART era, HCV-related liver disease (primarily end-stage liver disease) is a major cause of death among co-infected persons.^{105,106} HIV has been shown to accelerate progression of fibrosis among persons with chronic hepatitis C, including those with persistently normal ALT levels.^{107,108} Approximately, one-third of persons with HIV-HCV co-infection progress to cirrhosis over a 20 year period and about 50% will progress to cirrhosis over a 30 year period compared to 25% over 25 to 30 year period among mono-infected subjects.¹⁰⁹

Environmental factors

Alcohol—There are limited data on the prevalence of alcohol use among persons with chronic hepatitis C. A large meta-analysis of 111 studies which included 33,121 subjects, conducted to examine progression of fibrosis, reported that 19% of subjects consumed alcohol ranging from 20 g/day to 80 g/day.¹¹⁰ The prevalence of chronic hepatitis C appears to be 5–10 fold higher among persons with a history of alcohol abuse. Alcohol consumption is known to adversely affect the outcome of HCV infection: it has been associated with faster progression of liver fibrosis, higher frequency of cirrhosis, and increased incidence of hepatocellular carcinoma. Subjects with HCV who abuse alcohol have decreased survival as

compared with patients with either alcohol abuse or HCV liver injury alone. Alcohol consumption may be the single most important factor affecting disease progression in patients with chronic hepatitis C. Seeff et al. have reported that more than two thirds of deaths with end-stage liver disease secondary to non-A, non-B hepatitis occurred in alcoholic patients.⁴

An alcohol intake between 30–80 g/day has been shown to cause progression of liver disease.¹¹¹ In one study, mean fibrosis stage was significantly higher and progression of fibrosis higher in patients whose daily alcohol consumption was 50 g or more than in those who consumed less than 50 g, irrespective of age or duration of infection.¹⁹ A large meta-analysis conducted to explore the relationship between advanced liver disease and alcohol use taking into account the different definitions of heavy alcohol consumption across many studies, including more than 15,000 patients with HCV infection, demonstrated that heavy intake between 210 and 560 g/week was associated with a 2.3 fold increase risk of cirrhosis.¹¹² It was also shown that even moderate alcohol consumption, as low as 31–50 g/day in men and 21–50 g/day in women, might worsen histological activity and fibrosis in HCV-infected patients.¹¹³ The mechanism by which alcohol causes the progression of the disease is not very clear. Immune dysfunction, increased viral replication, emergence of HCV quasiespecies, apoptotic, steatosis and increased iron overload have been proposed.¹¹³ Currently, there is insufficient evidence to determine a “safe” amount of alcohol use. Therefore, despite the beneficial cardiovascular effects of light alcohol use (10–20 g/day), given the uncertainty on the effects of this amount of alcohol on liver disease progression, patients should be counseled of the adverse effects of alcohol on outcome of chronic hepatitis C and advised to refrain from alcohol use.

Smoking—Whether smoking has any effect on outcome of chronic hepatitis C is uncertain. Smoking >15 pack years was shown to be an independent predictor of liver fibrosis but this association was lost when disease activity was controlled for in a multivariate analysis.¹¹⁴ Tobacco use higher than 15 cig/day was associated with more severe histological activity in patients with chronic hepatitis C. In one study, the proportion of patients with moderate and marked activity (Metavir A2–A3) increased gradually from 62% in patients who did not smoke to 82% in patients who smoked more than 15 cigarettes/day 6 months before biopsy.¹¹⁵ Release of proinflammatory cytokines, lipid peroxidation, oxidative stress, steatosis and iron overload from secondary polycythemia are thought to be the mechanisms by which smoking causes progression of liver disease.¹¹⁶ Tobacco use is also known to independently contribute to the development of HCC. Indeed, alcohol, smoking and obesity act synergistically in the development of HCC.¹¹⁷ Although the evidence for smoking on outcome of HCV infection is weak, patients with chronic hepatitis C should be advised to not smoke.

Cannabis—There is both clinical and experimental evidence indicating that daily cannabis use is a co-factor modulating disease progression in patients with chronic hepatitis C. Several studies have reported a strong association between cannabis use and significant fibrosis (Metavir F3). In one study from France, 270 consecutive patients with chronic hepatitis C undergoing liver biopsy were studied. Categorizing cannabis use as none,

occasional or daily, daily cannabis use was associated with severe fibrosis on biopsy and a faster rate of fibrosis progression.¹¹⁸ The CB₁ receptor is widely expressed in the human liver and its up-regulation is associated with steatosis and advanced fibrosis.^{118–120} Furthermore, daily cannabis use and moderate to heavy alcohol use have additive effects in fibrosis progression.¹²⁰ Therefore, patients with chronic hepatitis C should abstain from use of cannabis.

Caffeine—Multiple epidemiological studies from different geographical regions have reported an association between daily caffeine consumption and lower risk of an elevated ALT level in persons without liver disease or at high risk for liver disease.^{121–123} Coffee consumption has also been associated with a lower risk of advanced liver disease, cirrhosis and hepatocellular carcinoma in patients with chronic liver disease. In one study, 177 patients scheduled to undergo liver biopsy were asked to complete a detailed caffeine questionnaire on three occasions over a 6-month period. Caffeine intake was correlated with severity of liver disease. A daily caffeine consumption >308 (equivalent to 2.25 cups/day) was associated with less severe hepatic fibrosis.¹²⁴ Interestingly, caffeine from other sources such as tea or caffeinated beverages was not associated with stage of liver fibrosis.¹²⁴ Although the evidence of the protective effects of coffee/caffeine on liver disease is growing, no prospective trials have been conducted on the use of caffeine/coffee to improve liver disease. In addition, since the amount of caffeine varies considerable from cup to cup of coffee the amount of caffeine that is required for a beneficial effect is unknown. Until more data is forthcoming we cannot recommend that patients with chronic hepatitis C use caffeine/coffee excessively.

Herbals—In the United States, silymarin (an extract of milk thistle) is the most popular herbal product used by persons with liver disease. The HALT-C trial examined the frequency and the potential effects of herbal supplements in a large cohort of patients with advanced chronic hepatitis C. Silymarin was found to be the most frequently used herbal supplement. Silymarin had no beneficial effect on ALT or HCV RNA levels but users reported fewer and milder symptoms of liver disease and better overall quality of life. Silymarin users had similar ALT and HCV levels to those of nonusers.¹²⁵ Further analysis of the HALT-C trial dataset demonstrated that silymarin use was associated with reduced progression to cirrhosis but had no impact on clinical outcomes.¹²⁶ Silymarin was also evaluated in a randomized controlled trial to improve disease activity using serum ALT as a surrogate in subjects who had previously failed interferon-based therapy. Higher than usual doses of silymarin had no benefit on reducing serum ALT levels in persons who failed to respond to prior interferon-based therapy and its use cannot be recommend in this population.¹²⁷ Another herbal compound, glycyrrhizin used in Japan was reported to lower ALT levels and also prevent carcinogenesis.¹²⁸ Currently, there is little evidence to support the use of herbals to improve outcome of chronic hepatitis C.

Conclusion

In conclusion, the natural history of hepatitis C virus is influenced by a wide variety of host, viral and environmental factors. Physicians should seek to identify these factors to risk

stratify patients. In addition, patients should be counseled to improve modifiable ones to limit disease progression.

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Key Points

- The incidence of chronic hepatitis C is declining in the United States but rates of cirrhosis and hepatocellular carcinoma are projected to increase over the next decade.
- Approximately 20–25% of subjects with chronic hepatitis C will progress to cirrhosis over 25–30 years.
- The outcome of chronic hepatitis C is highly variable and influenced by many host, viral and environmental factors, many of which cannot be modifiable

Figure 1.

Natural History of Hepatitis C Virus Infection.

Following exposure to hepatitis C virus, an acute hepatitis ensues. About 20% present with jaundice but the majority are asymptomatic. Spontaneous resolution occurs in 15–45%. The remainder develop a chronic hepatitis with a variable course. Cirrhosis develops in approximately 20–30% of subjects over a 25–30 year period. Once cirrhosis develops patients are at risk for hepatic decompensation, hepatocellular carcinoma and liver-related death.

Table 1

Factors That Affect The Natural History Of Chronic Hepatitis C

Host Factors	Viral Factors	Environmental Factors
Age at infection	Viral load	Alcohol
Gender	Genotype	Smoking
Race	Co-infection with HBV	Cannabis use
Obesity	Co-infection with HIV	Caffeine
Steatosis		
Insulin resistance		
Diabetes		
Genetics		
ALT levels		
Exercise		