Review

A Review of the Natural History of Chronic Hepatitis C Infection

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The burden of chronic hepatitis C infection worldwide is significant. Approximately 4.1 million people in the United States have anti-HCV antibodies. The prevalence worldwide varies, but reaches greater than 3.5% in some regions (North African, East Asia). The burden of hepatitis C virus is reflected in the morbidity and mortality of this disease, as well as the societal costs. The morbidity and mortality associated with chronic hepatitis c infection is mostly related to the rate of fibrosis and associated progression to cirrhosis. The natural history of this progression is a complex and dynamic process related to individual characteristics (age, sex, race, genetics), viral characteristics (genotype), behavioral (smoking, alcohol), metabolic factors (insulin resistance, obesity), and co-infection (Hepatitis B and HIV). This review describes the current literature on how these factors interact with chronic hepatitis C infection and impact the natural history of this disease and progression to fibrosis and cirrhosis.

INTRODUCTION

Chronic hepatitis C (HCV) is one of the most common liver diseases in the world and the leading cause of liver transplantation in the United States.   The prevalence worldwide ranges from as low as <1.5% (Latin America) to as high as >3.5% (North Africa, East Asia).[1] The prevalence of anti-HCV antibodies in the United States is approximately 1.6% (approximately 4.1 million people). The prevalence of positive HCV RNA is approximately 1.3% (approximately 3.2 million people). The peak prevalence occurs among persons born between 1945 and 1964 and the strongest risk factor for infection is a history of injection drug use.[2] The risk of chronic infection after an acute episode of hepatitis C is high. Studies have shown that after exposure to hepatitis C virus, 80 to 100 percent of patients remain HCV RNA positive, and 60 to 80 percent have persistently elevated liver enzymes.[3,4]

The age-adjusted mortality rate among patients with HCV in the United States in 2007 was 4.6 per 100,000 persons per year. This was higher than the mortality rate for HIV (4.2 deaths per 100,000 persons per year).[5] Furthermore, approximately 73% of these deaths occurred in individuals between the ages of 45 and 65 years.[5] The burden of chronic HCV has been shown to be significant in terms of mortality as well as in terms of societal costs. Chronic HCV accounts for approximately 8000-1300 deaths annually. Furthermore, projections show that between 2010 and 2019 there will be 165,900 deaths from chronic liver disease, 27,200 deaths from hepatocellular carcinoma, and $10.7 billion in direct

medical expenditures for HCV. Within this model, HCV was shown to lead to the loss of 1.83 million years of life in those younger than 65 and a societal cost of up to $54.2 billion.[6] The goal of this review is to discuss the natural history of HCV infection as well as the predictors of disease outcomes in chronic hepatitis C infection.

NATURAL HISTORY OF HEPATITIS C INFECTION

The majority of patients who acquire HCV do not spontaneously clear the virus and progress on to develop chronic HCV infection. However, defining the natural history of chronic HCV has been difficult because of the long course of the disease and often unknown timing of contracting the disease.[7] Ultimately, chronic HCV results in liver injury that may lead to fibrosis and variable progression to cirrhosis depending on the population. Multiple studies have shown that there are populations who do not progress.[8,9] Retrospective studies have demonstrated that the risk of developing cirrhosis may be up to 50 percent over 10-20 years in chronically infected patients. However, once advanced fibrosis has developed the annual rate of progression to cirrhosis is approximately 10 percent per year.[10-12]

The majority of morbidity and mortality associated with chronic HCV is seen in patients with cirrhosis.[13] Of note, not all patients with chronic HCV cirrhosis develop hepatic decompensation. Studies have shown the risk of developing hepatic decompensation to be 3.9% per year.[14] The development of cirrhosis is often silent and unrecognized in the majority of patients.[10] The physical examination may be remarkable for hepatomegaly (68%) or splenomegaly.[10] Laboratory findings which suggest progression to fibrosis

and cirrhosis include an elevated bilirubin (40%), hypoalbuminemia (10%), and decreased platelet counts.[15] An elevated alpha-feto protein (AFP) is concerning for development of hepatocellular carcinoma (HCC) and any patient with chronic HCV and an elevated AFP should undergo an ultrasound of their liver. However, up to 43 percent of patients with cirrhosis without hepatocellular carcinoma have a serum AFP between 10 and 100 ng/mL.[14-16]

The majority of deaths from HCV cirrhosis are related to complications from advanced liver disease. However, HCV cirrhosis accounts for approximately one-third of hepatocellular carcinoma cases in the United States and the risk of developing hepatocellular carcinoma once cirrhosis has been shown to be up to 3% per year.[14,17] The risk of developing HCC has been shown to be higher among certain HCV genotypes (genotype 1b).[18]

Table 1. Host, Viral, and Behavioural factors that impact disease progression of chronic hepatitis C infection.

Host	Viral	Behavioural
Age	Co-Infection (HIV, Hepatitis B)	Alcohol
Sex	HCV Genotype	Smoking
Metabolic (obesity, insulin resistance)		Coffee
Genetics		
Iron Deposition		

Factors impacting Disease Progression

There are multiple host-viral factors which have been shown to impact the progression of disease in chronic HCV. These factors include individual characteristics (age, sex, race, genetics), viral characteristics (genotype), behavioural (smoking, alcohol), metabolic factors (insulin resistance, obesity), and co-infection (Hepatitis B and HIV) (**Table 1**). Together, these factors impact the degree of fibrosis and progression to cirrhosis as well as the potential for development of hepatocellular carcinoma.

Age

Age is a known important host factor with respect to disease progression in HCV. However, it is difficult to differentiate age at acquisition from duration of HCV infection.

A younger age at time of initial infection has been shown to be protective with respect to progression of disease. This relationship remains after controlling for duration of infection.[8,19,20] Children who have contracted HCV vertically have repeatedly been shown to have very slow progression of liver fibrosis.[21,22] In one analysis, progression to cirrhosis over 20 years was much lower for those subjects infected before age 20 years (2%) versus those infected after age 50 years (63%).[8] A longer duration of the infection has also been associated with a higher grade of liver fibrosis.[23] The estimated probability of progression per year for men aged 61–70 years was 300-times greater than that for men aged 21–40 years.[24-26]

The precise reason for the variability in progression related to age is unclear. Paired biopsy studies have shown accelerated rates of fibrosis progression over time independent of age of acquisition.[24] Whether this progression comes with increasing duration of infection or with increasing age is unclear. Another plausible possibility is decreasing rates of fibrosis regression with age.[27-28]

Sex

There appears to be more rapid progression to cirrhosis in males.[29] Males have been shown to have a rate of progression towards fibrosis 10-times higher than that of females independent of age.[25] This increased rate of disease progression has been shown after controlling for age, duration of infection, alcohol consumption, and metabolic factors.[30] Female gender appears to be protective in terms of disease progression, suggesting that hormonal factors may be important in the regulation of liver fibrosis.[31] In fact, estrogen has been shown in multiple studies to play a role in progression to fibrosis. Estrogen has not only been shown to inhibit proliferation and activity of stellate cells responsible for fibrogenesis,[32] but also to inhibit IL-6 production by Kupffer cells. The latter has been found to be a potential etiology of increased rates of HCC seen among men versus women.[33]

Race

Approximately 3.2 million persons in the United States have chronic HCV.[34,35] African Americans comprise approximately 13% of the US population, but make up approximately 23% of Americans with HCV.[36] A report using NHANES III data (1999-2002) demonstrated that the rate of a positive HCV antibody test was higher in blacks than in whites (3.2% versus 1.5%). Within this analysis, Black men had higher rates of infection, with the highest prevalence rate of 9.8% among black men ages 40 to 49 years.[37,38] Latinos are the largest growing minority population in the United States and are estimated to represent 25% of the US population by the year 2050. While the prevalence of HCV in whites within the United States is estimated at 1.5%, the prevalence among Latino's is estimated at 2.6%.[2] Although the prevalence of HCV appears to be higher among African Americans, the natural progression of the disease may be less severe when compared to whites. Conversely, there is evidence that the progression of HCV may be more aggressive among Latino's.

Among African Americans, the histological activity and the incidence of liver cirrhosis is lower than in Caucasians.[39] When compared to their white counterparts, African Americans have been found to have lower rates of fibrosis,[40] lower alanine aminotransferase (ALT) levels, and reduced inflammatory activity scores on liver biopsy.[41] While African Americans appear to have a favorable profile with respect to disease progression when compared to whites, Latinos have been found to have an unfavorable profile. Latino patients in the US have a faster progression to cirrhosis when compared to whites.[42] Asians appear to have a similar disease course as whites.[43] An important host factor that is impacted by race is the prevalence of IL28B polymorphisms. Single-nucleotide polymorphisms near the interleukin 28B gene (IL28B) have been associated with a two-fold improvement in response to

treatment with interferon. This polymorphism has a greater frequency in European than African populations, and explains approximately half of the difference in response rates between African-Americans and patients of European ancestry.[44]

Metabolic Factors

The prevalence of hepatic steatosis in the United States has been found to be as high as 30-35% among potential liver donors on biopsy.[27,45] The occurrence of hepatic steatosis among individuals with HCV is suggested to be as high as 50%–65%.[46] Hepatic steatosis has been found to be associated with increased severity of necro-inflammatory activity[47,48] as well as fibrosis.[48] The cumulative incidence of HCC has also been found to be higher in the setting of steatosis.[49] The relationship between steatosis and disease progression in HCV appears to be genotype specific. Hepatic steatosis has been found more frequently and is more severe in the setting of genotype 3 infection versus genotype 1 and 2 infection.[50]

Insulin resistance and diabetes may play a significant role in disease progression in HCV. The presence of insulin resistance has been shown to lead to more severe fibrosis.[51,52] and decreased response to therapy.[53] While there is evidence that insulin resistance may impact disease progression in HCV, the relationship is confounded by other known factors which impact disease progression and are closely correlated with diabetes (age, BMI).[54]

Iron

The underlying pathophysiology of liver damage from HCV is related to oxidative stress. The mechanism for oxidative stress includes activation of pro-oxidant enzymes, weakening of antioxidant defenses, organelle damage, and metals unbalance.[55] A crucial step early in the HCV related oxidative stress process is mitochondrial damage. Mitochondria play a crucial role in energy metabolism and metal homeostasis, primarily iron and copper. Mitochondria are a target for the hepatitis C virus because many HCV proteins associate with mitochondria during the life cycle of the virus.[55] The impact that HCV has on mitochondria and metal homeostasis (mainly iron and copper) may partly explain the well-established impact that iron deposition has on the natural history of HCV. Iron overload has been shown to occur in up to 40% of patients with HCV and has been associated with accelerated fibrosis.[27,56,57] Iron deposition may also partly explain gender differences between males and women of reproductive age. Furthermore, there is evidence that the immune response of HCV to interferon is impacted by iron deposition. In the setting of mono-therapy with interferon, a decreased response has been shown in those individuals with iron overload on biopsy.[58,59] Patients with HCV and either hereditary or secondary hemochromatosis have been shown to have accelerated fibrosis[60] and phlebotomy has been shown to lower ALT (but not response rate) in patients with iron on liver biopsy.[61,62] Finally, iron overload syndromes are well known non-viral causes of hepatocellular carcinoma, either in combination with viral illnesses (HCV or HBV) or individually (hereditary hemochromatosis).[63-64]

Behavioral Factors

Both alcohol and smoking impact disease progression in chronic HCV. Alcohol consumption is an independent risk and significant risk factor the development of cirrhosis in the setting of HCV. Intake of more than 50g of alcohol daily is associated with increased risk of liver cirrhosis in HCV infected patients.[8,65,66] Interestingly, there are contradictory studies which have shown a protective effect for in the setting of drinking small amounts of alcohol. Smoking may also be an independent risk factor for development of cirrhosis with chronic HCV. The use of cigarettes has been shown to predict progression to fibrosis in patients with CHC.[67,68] Similarly, the use of daily cannabis has also been shown to be a predictor of fibrosis progression in CHC 1.[69] Conversely, the consumption of coffee has been shown to have a protective effect. Consumption of 3 or more cups of coffee daily has been shown to result in a lower grade of liver fibrosis, decreased steatosis, reduced insulin resistance, and lower ALT levels.[70] Not only does coffee consumption improve overall mortality in population based studies,[71] but it also impacts responses to HCV treatment.[72] Increased coffee intake has been found to increase the likelihood of SVR to antiviral treatment with PEG-IFN and RBV.[72]

Co-infection

Co-infection with HIV and Hepatitis B virus (HBV) has been shown to impact progression of disease in chronic HCV. HIV appears to impact both immunity and progression of disease in the setting of HCV.[27] With respect to immunity, HIV+ individuals have quantitative and qualitative abnormalities of their CD4 T cells.[73] This results in reduced ability of CD4+ T cells to help viral specific CD8+ T cells. Hence, the hepatitis C virus in this setting benefits from a reduced viral-specific CD8+ T cell response. Hence, HIV infected individuals con-infected with HCV have greater difficulty controlling their HCV viral loads.[74] Co-infection with HIV has also been shown to impact disease progression. Patients co-infected with HIV and HCV have more rapid fibrosis progression than mono-infected patients controlling for multiple disease factors known to accelerate fibrosis (age, sex, alcohol consumption).[24,75] There is also evidence that HIV co-infection results in higher HCV plasma RNA viral loads and increased HCC.[27,76,77] While HIV co-infection may double the risk of cirrhosis and increase the risk of decompensated liver disease by a factor of 6,[78] it appears that HAART therapy may reduce liver related mortality.[79]

Co-infection with HBV and HCV is quite common and likely underestimated due to the potential for occult HBV infection.[27,80] Co-infection of HBV and HCV typically results in dominance by one virus and suppression of the other.[81] Regardless, the presence of chronic HBV infection in the setting of chronic HCV has been shown to increase ALT level, result in more rapid development of cirrhosis, and increase the risk of HCC.[81,82]

Genetic Factors

The excess accumulation of extracellular matrix proteins resulting in fibrogenesis is mediated by necro-inflammation and activation of stellate cells.[83] Variation in expression of various mRNA's and miRNA's has been shown to impact fibrosis expression.[84] Multiple small nuclear polypeptides SNPs have been found to increase fibrosis and progression to cirrhosis in chronic HCV. Matrix metalloproteinases (MMPs) play an important role in fibrosis progression and SNPs for both MMP-1 2G homozygote and MMP-9 C allele were more frequent in HCV patients with cirrhosis than in those without cirrhosis.[85,86] Similarly, recent studies have shown the association of AZIN1 SNP with rapid progression of fibrosis and an allele that delays fibrogenesis through alternative splicing of AZ1N1.[87] Furthermore, a sequence variation in the patatin-like phospholipase-3 (PNPLA3) has been shown to be strongly associated with high risk of steatosis as well as fibrosis and fibrosis progression in patients with chronic HCV.[88] A seven SNP variant signature has been identified that is associated with the risk of development of advanced fibrosis in chronic HCV infection as well as estimated fibrosis progression rate.[89] This cirrhosis risk score (CRS) has been independently validated in small longitudinal cohorts to predict patients with and without progression.[90] Low 25-OH vitamin D levels and common genetic variations in the vitamin D receptor gene are also associated with fibrosis progression.[91]

Review of the literature shows that various SNPs are likely associated with fibrosis progression and several extra-cellular-matrix and chemokine mRNAs are probably upregulated in patients with more advanced fibrosis.[84] However, many of these proposed host genetic factors have not been validated in independent cohorts. Another limitation is that prior studies mostly relied upon cross-sectional and not paired biopsy evaluation, for determination of disease risk and progression. More research is required to better understand the precise host genetic mechanisms involved in progression of chronic HCV. Nonetheless, it is clear that underlying genetics within an individual can impact progression of fibrosis and cirrhosis in chronic HCV infection.

Viral Factors

There is data to support the role of viral factors in the natural history of chronic HCV infection and treatment response. Of note, viral factors do not appear to impact spontaneous HCV clearance.[92] The studies attempting to further elucidate this relationship have been limited by the difficulty in collecting and characterizing large cohorts of patients soon after seroconversion.[93] While the role of viral factors in fibrosis progression is still debated for the immunocompetent mono-infected patient, there is evidence to support that HCV genotype may play a role in fibrosis progression. Using a large cohort, Bochud et al 2009 showed that HCV viral genotype-3 was associated with increased rate of fibrosis progression independent of other epidemiological risk factors.[94] This would correlate with data that has shown increased mortality with genotype 3.[95] Multiple studies have shown that viral load does not appear to have an impact on

disease progression.[27] Potential mechanisms through which HCV results in increased fibrosis may not be immune related. For example, there are conflicting data in regards to the role of HLA class I and II polymorphisms and fibrosis progression.[96-98] However, there is data to suggest HCV mediated activation of stellate cells through promotion of steatosis, oxidative stress, and apoptosis may play a role.[99,100]

HCV viral genotype does predict HCV treatment response. The SVR rates among treatment naive individuals with HCV genotype-I using PEG-IFN/RBV are 40-50%. Conversely the rates using PEG-IFN/RBV are as high as 75% in genotypes 2 and 3 infection.[93,101] In the setting of new direct-acting antivirals, SVR rates for genotype-1 are now approaching those of genotype 2 and 3.[102] However, of note, genotype subset is also an important predictor of treatment response. Among both telaprevir and boceprevir regimens, SVR rates are approximately 10% lower for HCV genotype-1a compared to genotype-1b.[103] The role of emergent resistance mutations in disease progression amongst patients with incomplete virologic responses to the interferon-sparing oral regimens has not been established.

Mode of Transmission

The role of mode of transmission in disease progression of chronic HCV remains controversial. Initially there was concern that acquiring HCV through a blood transfusion was associated with higher rates of cirrhosis than seen in the setting of community acquired or childhood acquired HCV.[104] One large retrospective analysis showed the prevalence of cirrhosis to be 54% among those who contracted HCV through a blood transfusion, versus 21% for those who contracted HCV via IV drug abuse.[27,105] These findings raised the possibility that the mode of transmission, perhaps via the size of the inoculum, dictated the risk of progressing to fibrosis. However, subsequent studies have refuted these findings. When correcting for age, other analyses have shown there was no significant difference in development of cirrhosis regardless of mode of transmission.[24] Mode of acquisition appears to have a limited impact on outcomes, with similar viral clearance and anti-HCV antibody seroconversion rates in vertical and transfusion acquired infection.[106] More research on the potential role of mode of transmission is required. Whether mode of transmission and size of the inoculum are predictive of disease progression is currently unclear.

CONCLUSION

Chronic HCV infection results in significant morbidity and mortality worldwide. We have provided an overview of the various factors known to have a potential impact on the natural history of chronic HCV infection. While the role of some factors is clear and established (Age, Race, Sex, Co-infection with HIV), others still require further research (genetics, smoking, genotype, mode of transmission). Ultimately, better understanding of host-viral and environmental factors as they relate to the patient will allow for the health care provider to consider potential modifiable disease risk factors and provide an individualized approach to management. Within the past few years there has been rapid

evolution of novel innovative antiviral therapies in HCV infection, including new interferon-sparing direct-acting antivirals (DAA's) regimens. These new medications appear safe, well-tolerated and with high efficacy across genotypes, and represent the opportunity for curing hepatitis C in the majority of diagnosed patients, even in populations where cure rates were previously low with prior standard-of-care therapy. However, most chronic HCV patients remain undiagnosed, and there are still unresolved socioeconomic issues regarding the significant cost and availability of these new regimens. Thus, a better understanding of the natural history of disease progression within the individual will also allow for a tailored approach to treatment related decisions using these emerging medication regimens.

CONFLICT OF INTEREST
None.

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