Clinical manifestations and natural history of chronic hepatitis C virus infection

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INTRODUCTION

Following infection with the hepatitis C virus (HCV), chronic infection typically occurs, with approximately 50 to 85 percent of cases developing chronic hepatitis. However, chronic HCV infection is usually slowly progressive and may not result in clinically apparent liver disease in many patients. Approximately 5 to 30 percent of chronically infected individuals develop cirrhosis over a 20- to 30-year period of time.

In the United States, chronic HCV is the most common cause of chronic liver disease and the most frequent indication for liver transplantation.

This topic will review the clinical features associated with chronic HCV infection and factors associated with the progression of chronic liver disease. Acute HCV infection and the epidemiology, diagnosis, and treatment of chronic HCV infection are discussed separately. (See "Epidemiology and transmission of hepatitis C virus infection" and "Screening and diagnosis of chronic hepatitis C virus infection" and "Overview of the management of chronic hepatitis C virus infection".)

CLINICAL FEATURES

Although many patients with chronic HCV infection are symptomatic, most symptoms are nonspecific and not clearly a result of HCV infection itself. Even if cirrhosis develops, many patients have only nonspecific symptoms. Occasionally, patients have specific extrahepatic findings (such as cryoglobulinemia, renal disease, or specific dermatologic disorders) that are directly related to HCV infection.

Generalized symptoms — Patients with chronic HCV infection often have a high symptom burden, but the extent to which HCV infection itself, rather than comorbid conditions, contributes to the symptoms is unclear. The most frequent complaints are fatigue and sleep disturbances; other symptoms include nausea, diarrhea, abdominal pain, anorexia, myalgia, arthralgia, weakness, and weight loss [1]. Neuropsychiatric symptoms (eg, depression and anxiety) are also common.

However, the symptoms of chronic HCV infection are not necessarily specific to the infection itself. In one study of 100 patients with chronic HCV infection without cirrhosis, fatigue was the most common self-reported complaint, but it occurred with similar frequency among 100 healthy blood donor controls without HCV infection (62 versus 70 percent in controls) [2]. Abdominal pain, itching, and dark urine were the only complaints that were more common among the HCV-infected patients, although they were present in only a small number of patients. In a subsequent study of 1600 patients with chronic HCV infection, although symptoms were highly prevalent and often severe, symptom burden was more strongly associated with demographic, socioeconomic, and psychiatric features than markers of liver inflammation or fibrosis [1].

Nevertheless, the symptoms may lead to a decrease in the quality of life [3], which may in part be accounted for by awareness of infection [4], and which can be improved following successful treatment [5]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'Benefits of treatment'.)

HCV infection has also been associated with cognitive impairment, which has been demonstrated in patients with HCV independent of the severity of liver disease [6-9]. The mechanisms leading to the impairment are not well understood.

Extrahepatic manifestations — A number of extrahepatic diseases have been associated with chronic HCV infection. Most cases appear to be directly related to the viral infection. These include:

- Hematologic diseases, such as essential mixed cryoglobulinemia and lymphoma
- Renal disease, particularly membranoproliferative glomerulonephritis
- Autoimmune disorders, such as thyroiditis and the presence of autoantibodies

- Dermatologic conditions, such as porphyria cutanea tarda and lichen planus
- Diabetes mellitus

The frequency of such findings is uncertain, however they are not uncommon. In one series of 321 patients, at least one extrahepatic manifestation was observed in 38 percent (table 1) [10]. These are discussed in detail elsewhere. (See "Extrahepatic manifestations of hepatitis C virus infection".)

Laboratory findings

Serum aminotransferases — There is wide variability in serum aminotransferase levels among individual patients with chronic HCV infection over time. Up to one-third of patients have a normal serum alanine aminotransferase (ALT) [11]. Slight enzyme elevations are usually seen in the remaining patients; only about 25 percent have a serum ALT concentration more than twice normal, and it is rare to find elevations more than 10 times normal.

Occasionally, acute increases in the serum aminotransferases can occur during chronic HCV infection without apparent alternate cause. This phenomenon is not well defined, and so the incidence is difficult to assess. (See 'Acute exacerbation of chronic infection' below.)

There is generally a poor correlation between aminotransferase levels and liver histology [12,13]. As an example, a study of 90 patients with chronic HCV infection found no correlation between histologic findings and serum ALT values unless the ALT was elevated more than 10-fold; these marked elevations were associated with periportal inflammation and necrosis (so-called piecemeal necrosis) [12]. The mean values of aminotransferases were significantly lower among patients with chronic persistent hepatitis (minimal activity) than those with chronic active hepatitis (mild to moderate activity); however, overlap of values was considerable between the different histologic groups. Patients with normal serum ALT almost always show histologic evidence of chronic inflammation, although the degree of injury is typically minimal or mild [2,11,14].

Despite the lack of direct correlation between liver histology and serum ALT concentrations in chronic hepatitis C, aminotransferase levels have been incorporated into formulas that are used as noninvasive markers of liver fibrosis. These are discussed in detail elsewhere. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic tests and imaging examinations", section on 'Serologic tests'.)

Viral levels — During chronic HCV infection (ie, following the acute phase), viral levels of HCV remain generally constant, although significant fluctuations can occur [15-17]. A retrospective study of 818 HCV-infected individuals, the majority of whom were also HIV-infected, evaluated

changes in HCV viral levels checked over a mean of five and a half years [15]. Variations in HCV viral load >1 log occurred in 15 percent and variations >0.5 log in 44 percent. Overall, the viral level has modest clinical significance. There is little correlation between HCV viral levels and serum aminotransferase levels or the severity of liver disease [18-20]. However, the viral level may influence the optimal duration of certain antiviral regimens.

The variables that affect viral levels are not well elucidated. Coinfections with other viruses have been observed to impact the serum levels of HCV ribonucleic acid (RNA). HCV levels generally increase following HIV infection [21,22]. On the other hand, a persistent decline in HCV RNA replication can occur following acute hepatitis B virus (HBV) infection [23]. Nevertheless, coinfection with either HIV or HBV is associated with a faster rate of fibrosis progression. (See 'Host factors' below.)

Other — Other laboratory manifestations that can be observed in chronic HCV infection include those that are related to the potential extrahepatic manifestations of HCV. As examples, low platelets may reflect immune-mediated thrombocytopenia; a reactive rheumatoid factor, an increased production of autoantibodies; and proteinuria and/or microscopic hematuria, glomerulonephritis. These are discussed in detail elsewhere. (See "Extrahepatic manifestations of hepatitis C virus infection".)

Findings in cirrhosis — Approximately 5 to 30 percent of chronically infected individuals develop cirrhosis over a 20- to 30-year period of time, although slower and faster rates of progression have been described (see 'Risk and rate of progression to cirrhosis' below). The development of cirrhosis is silent in the majority of patients in whom it occurs [24]. Although these patients tend to be more symptomatic than those with chronic hepatitis alone, no clinical symptom, physical sign, or laboratory test is either sensitive or very specific for the diagnosis. The physical examination may reveal hepatomegaly (68 percent in one series) or splenomegaly [24]. In our experience, however, most patients with cirrhosis do not have hepatomegaly. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Symptoms' and "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Physical examination'.)

Laboratory testing can be helpful in identifying cirrhosis in HCV-infected patients, but none are 100 percent specific. Suggestive findings include an elevation in the serum bilirubin concentration, hypoalbuminemia, or a decrease in the platelet count [25,26]. (See "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Laboratory findings'.)

The serum alpha fetoprotein (AFP) concentration may be mildly elevated in chronic HCV infection and does not necessarily imply the presence of hepatocellular carcinoma or cirrhosis.

Up to 43 percent of patients with cirrhosis without hepatocellular carcinoma have a serum AFP between 10 and 100 ng/mL [27,28]. Nevertheless, an elevated serum AFP concentration requires imaging of the liver to rule out hepatocellular carcinoma. Serial testing for several months is warranted if the imaging studies are negative since rising levels may be indicative of an occult malignancy. (See "Surveillance for hepatocellular carcinoma in adults", section on 'Patients with cirrhosis'.)

NATURAL HISTORY

The majority of patients who acquire HCV do not spontaneously clear the virus and thus develop chronic HCV infection. Chronic infection results in liver fibrosis and ultimately cirrhosis in a subset of patients, although the rate of disease progression is variable. Patients who develop cirrhosis are at further risk for complicating events (such as variceal hemorrhage, ascites, and encephalopathy) and hepatocellular carcinoma, although many patients with compensated cirrhosis remain stable for years (algorithm 1).

Risk of chronic infection — The risk of chronic infection after HCV acquisition is high. In most studies, 50 to 85 percent of patients chronically remain HCV RNA positive following infection and seroconversion, depending on the population and the source of infection (algorithm 1) [29]. Of those who are able to spontaneously clear HCV, most do so within 12 weeks of seroconversion, although spontaneous clearance after a longer period of follow-up has been described [29]. These issues are discussed in detail elsewhere. (See "Clinical manifestations, diagnosis, and treatment of acute hepatitis C virus infection in adults", section on 'Spontaneous viral clearance'.)

The mechanism responsible for the high prevalence of viral persistence, and thus chronic infection, is unclear, but both viral and host factors are likely to contribute.

Viral predictors of risk — HCV has a tendency toward rapid mutation, which leads to extensive viral diversity among the viral populations infecting a single host. This can contribute to viral persistence, as the viral diversity allows HCV to escape immune recognition [30]. (See "Characteristics of the hepatitis C virus", section on 'Viral heterogeneity'.)

Host predictors of risk — Host factors may also be involved in the ability to spontaneously clear the virus. One of the most influential factors appears to be certain polymorphisms of a chromosomal locus close to the interleukin-28B (IL28B) gene [31-33]. In one report of 1008 patients, the presence of the favorable (C/C type) allele at this locus was associated with clearance rates of approximately 50 to 55 percent compared with only 16 to 20 percent in

patients with the unfavorable (T/T type) allele [31]. The favorable alleles were more common in patients of European ancestry compared with those of African ancestry. A second study that included 284 patients with chronic HCV infection and 69 patients who had spontaneously cleared the virus found that the favorable allele was present in 73 percent of patients who spontaneously cleared the virus, compared with 46 percent of patients with persistent infection [34]. These polymorphisms are also an important predictor of response during treatment with peginterferon and ribavirin.

Black individuals are less likely than White individuals to have the favorable allele, and data suggest they may be less likely to spontaneously clear the virus. In a population-based study, 9 percent of Black persons and 27 percent of White persons were anti-HCV positive and HCV RNA negative [35]. However, a limitation of the study is that information on which patients received treatment was not available, so these numbers likely overestimate the rate of spontaneous clearance.

Other factors that have been associated with a higher likelihood of spontaneous clearance include:

- The presence of specific HLA-DRB1 and DQB1 alleles [36]
- High titers of neutralizing antibodies against HCV structural proteins [37]
- Host neutralizing responses that target viral entry after HCV binding [38]
- The persistence of an HCV-specific CD4 T-cell response [39]
- White patients with relatively low peak levels of HCV viremia during acute infection [40]
- Female sex [29]
- Infection during childhood [41]
- Symptomatic acute infection [42]

Acute exacerbation of chronic infection — Acute exacerbation of chronic HCV infection, with a significant elevation of serum aminotransferase levels over the baseline level in the absence of other potential causes of acute hepatitis, can occur. However, this phenomenon is not well characterized, and there are no standard definitions for it. Thus, its true incidence is unknown. Widely fluctuating aminotransferases were reported frequently in early studies on HCV, with an approximate incidence of ten percent [43].

In a study from Italy of 82 patients with chronic HCV infection who were identified as having a symptomatic five-fold or greater increase in the alanine aminotransferase (ALT) level over baseline without an alternative cause of acute hepatitis, ALT levels returned towards baseline within five months in the majority, but some patients had recurrent flares and others had persistent elevation of the ALT [44]. Genotype 2 infection was present in 46 percent,

disproportionately greater than the historically estimated prevalence of 20 percent for that genotype in Italy. An earlier study from Italy had also suggested an association of genotype 2 with acute exacerbations [45].

Presumptive acute exacerbations of chronic HCV have also been described following receipt of immunosuppressive agents. In a retrospective study of 308 patients with cancer and chronic HCV infection, 11 percent were identified as having a three-fold or greater increase in the baseline ALT level without an alternative explanation [46]. Presence of a hematologic tumor and receipt of rituximab were independently associated with such an ALT increase. However, drug induced hepatotoxicity could not be ruled out.

Such increases in the aminotransferase levels may be associated with more rapid progression of liver disease. Among 23 of the 82 patients in the case series from Italy who underwent paired liver biopsies, a greater proportion had progression of fibrosis and inflammation over time (78 and 61 percent, respectively) compared with an age-, sex-, and genotype-matched control group who did not experience an increase in the ALT level (39 and 10 percent, respectively) [44].

Risk and rate of progression to cirrhosis — The natural history of chronic HCV infection has been difficult to clearly define because of the long course of the disease, the difficulty in measuring precise duration of infection, and other factors that can affect disease course. A systematic review of 111 studies analyzing the natural history of HCV infection estimated that the prevalence of cirrhosis 20 years after infection was 16 percent (95% CI 14-19 percent) [47]. Estimates of the rate of cirrhosis development, however, have varied widely, in part because of the different study populations that may have had variable risk factors for fibrosis progression [24,48-63] (see 'Factors associated with disease progression' below). Additionally, estimates from retrospective studies (17 to 55 percent) have been higher than prospective studies (7 to 16 percent), possibly reflecting referral bias in the retrospective studies.

Studies of patients who presented clinically with chronic hepatitis tend to report a more aggressive course with a high risk of cirrhosis (and subsequent consequences of decompensation and hepatocellular carcinoma) [24,52,54]. In one series from the United States, 131 patients with chronic post-transfusion HCV infection were evaluated a mean of 22 years after transfusion: 23 percent had chronic active hepatitis and 51 percent had cirrhosis [24]. It was estimated that the mean time to develop cirrhosis was 20.6 years.

However, other studies have suggested slower rates and a lower risk of progression to cirrhosis [53,55-59,64]. In a large French series, the mean time to cirrhosis was 30 years [53]. It was estimated that 31 percent of patients would show no evidence of cirrhosis for at least 50 years. Even slower rates of progression were noted in another cohort study that followed 1980 women

in Germany who had been infected with contaminated batches of anti-D immune globulin [65]. After 25 years, overt cirrhosis or advanced fibrosis had developed in only 0.5 and 1.5 percent of the cohort, respectively, while only one patient had been diagnosed with hepatocellular carcinoma [65]. By 35 years of follow-up, the prevalence of cirrhosis, as detected by ultrasound, increased to approximately 14 percent among the 305 women who remained in the cohort and remained viremic (were either treatment-naïve or had failed treatment) [66]. Similarly, in a study that used serial liver biopsies to assess fibrosis rate among 184 women in Ireland who had received HCV-contaminated immunoglobulin, 49 percent showed no change in fibrosis, 24 percent showed regression, and 27 percent showed progression of fibrosis over more than 10 years of follow-up [64,67].

The reason for differences in the susceptibility to disease progression among individual patients is incompletely understood. Host and viral factors that may be significant are discussed elsewhere. (See 'Factors associated with disease progression' below.)

Nevertheless, once an individual has developed advanced fibrosis (ie, bridging fibrosis or METAVIR stage F3), the risk of progression to cirrhosis is high, approximately 10 percent per year [68]. (See 'Liver histology' below.)

Hepatic decompensation — Hepatic decompensation is characterized by the development of certain liver-related complications, including ascites, variceal bleeding, and encephalopathy. In patients with chronic HCV infection, jaundice is almost always a sign of advanced liver disease. Almost all HCV-infected patients who develop these complications have cirrhosis; however, not all patients with cirrhosis develop these complications [28,69,70]. A study of 384 patients with compensated cirrhosis due to HCV found that the risk of developing hepatic decompensation was 3.9 percent per year [28]. The most common form of decompensation was ascites.

Similarly, in the large prospective Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial, which included 1050 HCV-infected patients with either advanced fibrosis or cirrhosis, there were 679 liver-related outcomes over eight years of follow-up [68]. The most common events were CTP score ≥7 and definite/presumed hepatocellular carcinoma; the other outcomes were variceal hemorrhage, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, liver transplantation, or death. Clinical outcomes were more common among patients with cirrhosis compared with those with advanced fibrosis (7.5 versus 3.3 percent per year). Once a patient developed a CTP score ≥7, the rate of subsequent clinical events increased to 12.9 percent per year, with a mortality rate of 10 percent per year.

Once complications of cirrhosis have occurred, liver transplantation is the only effective therapy. Recurrent HCV infection of the graft occurs in almost all patients, although the long-term

survival after transplantation for HCV is similar to that for other causes of hepatic failure (60 to 80 percent). (See "Hepatitis C virus infection in liver transplant candidates and recipients".)

Prognosis of decompensated liver disease in general is discussed in detail elsewhere. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Prognosis'.)

Hepatocellular carcinoma — HCV-associated mortality is more likely to be due to end stage liver disease rather than hepatocellular carcinoma. Nevertheless, in the United States, HCV accounts for approximately one-third of hepatocellular carcinoma cases. Estimates of the risk of developing hepatocellular carcinoma once cirrhosis has developed have varied from 0 to 3 percent per year in various reports [28,69]. The risk appears to be greater with genotype 1b compared with genotypes 2a/c, although this observation may be confounded by other factors [71]. (See 'Viral factors' below.)

In contrast to hepatitis B virus infection, hepatocellular carcinoma in patients with HCV occurs almost exclusively in those with cirrhosis, suggesting that cirrhosis is the major risk factor. One study found that obesity may also be an independent risk factor [72]. There is also suggestive experimental evidence that HCV infection itself can promote the development of hepatocellular carcinoma. Mice that were made transgenic for the HCV core gene developed adenomas and subsequent carcinoma within the adenomas [73]. (See "Epidemiology and risk factors for hepatocellular carcinoma".)

Survival — Overall survival is decreased in patients with chronic HCV infection, especially in those who have developed cirrhosis. In 2007 in the United States, the age-adjusted mortality rate among patients with HCV infection was 4.6 per 100,000 persons per year, a rate that was higher than that seen for HIV (4.2 deaths per 100,000 persons per year) [74]. An estimated 8000 to 13,000 deaths occur each year in the United States from chronic HCV infection.

Compared to uninfected patients, patients with chronic HCV infection are more likely to die at a younger age and, as expected, from liver-related causes [74-76]. In the report above of HCV-associated mortality in the United States, 73 percent of the deaths were in patients between the ages of 45 and 65 years [74]. Similarly, in an analysis of death records in New York City from 2000 to 2011, the median age at death of over 13,000 individuals with HCV infection was 60 years, compared with 78 years among over 600,000 individuals without HCV or HIV infection [75]. HCV-infected individuals were more likely to have died from liver cancer (OR 9.2), drug-related causes (OR 4.3), and cirrhosis (OR 3.7), compared with uninfected individuals.

Mortality increases with progression of liver disease. In the large prospective Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial, which included 1050 patients

with advanced fibrosis or cirrhosis who were followed for a median of 5.7 years, 122 patients (12 percent) died and an additional 74 patients (7 percent) underwent liver transplantation [77]. The majority of deaths (62 percent) were attributed to liver-related causes. The mortality rate was higher among patients with cirrhosis compared with those who had advanced fibrosis (14 versus 7 percent). In a series of 384 patients with compensated cirrhosis, the 3, 5, and 10-year survival rates were 96, 91, and 79 percent, respectively [28]. Once decompensated cirrhosis occurred, the five-year survival fell to 50 percent. Other studies have found similarly low survival rates following a diagnosis of decompensated HCV-related cirrhosis [69,70]. Survival may also be worse in patients who develop cryoglobulinemia [78].

Causes of death among patients with HCV are not always related to liver disease and may vary based upon the age group being examined [75,79,80]. As an example, in a population study from Denmark, the primary cause of death among patients with HCV aged 20 to 39 years was unnatural (reported as death due to mental and behavioral disorders related to psychoactive substance use and death resulting from external causes) [80]. The 10-year risk of unnatural death in patients with HCV between the ages of 20 and 29 years was 13 percent. In patients between the ages of 40 and 59 years, deaths were equally distributed between liver-related, non-liver-related, and unnatural causes. In patients 70 years of age or older with HCV, the most common causes of death were non-liver related. Patients with HCV were at increased risk of death compared with non-HCV-infected individuals at all ages, ranging from an 18-fold increase for 20- to 29-year-olds, to a 1.6-fold increase for patients aged 70 years or greater.

FACTORS ASSOCIATED WITH DISEASE PROGRESSION

Several factors appear to be important determinants of fibrosis progression in individual HCV-infected patients, including baseline liver histology, age, ethnic background, sex, alcohol use, comorbidities such as obesity or viral coinfection, and HCV-specific cellular immune response. As examples, young women and children infected with HCV tend to have slower rates of fibrosis progression. However, even in a relatively homogeneous population such as in a study of Irish women who received contaminated immune globulin [64], the outcome is not uniform, suggesting that unexplained factors influence the disease.

Liver histology — The best clinical predictor of future disease progression in chronic HCV infection is the amount of baseline inflammation and fibrosis on liver biopsy or by noninvasive measurements [81,82]. This relationship was illustrated in a study of 70 patients with chronic HCV infection (figure 1) [81]:

- Patients with mild inflammation (portal inflammation alone or with only focal periportal extension) and no fibrosis had only a 1.2 percent annual risk of progressing to cirrhosis.

- Patients with moderate chronic hepatitis (periportal inflammation usually involving more than 30 percent of the limiting plate) had a 4.6 percent annual risk of developing cirrhosis; more than 90 percent developed cirrhosis within 20 years of the time of the biopsy (which was not the onset of infection).

- Nearly all patients with severe inflammation or bridging fibrosis developed cirrhosis within 10 years.

In addition, improvement in inflammation on follow-up biopsy is also associated with less fibrosis progression [83].

Hepatic fat accumulation also appears to adversely affect liver fibrosis. Moderate to severe steatosis on baseline biopsy has been associated with more rapid progression to advanced fibrosis and may be associated with insulin resistance in the absence of obesity or diabetes mellitus [84,85]. Genotype 3 infection is also associated with an increased risk of hepatic steatosis, possibly related to direct effects on lipid metabolism in liver cells [86]. However, the relationship between steatosis and clinical outcomes is complex. In a study of 985 patients in a study of long-term interferon treatment for chronic HCV, the presence of steatosis on a baseline biopsy was associated with worse clinical outcomes in those with bridging fibrosis while lower rates of adverse clinical outcomes were observed among those with steatosis and cirrhosis at baseline [87].

Stainable iron in hepatocytes has also been shown to predict progression and clinical and histologic outcomes in patients with advanced chronic hepatitis C [88].

Liver stiffness, as measured by transient elastography, reflects underlying fibrosis and has also been associated with prognosis of liver disease. This is discussed in detail elsewhere. (See "Noninvasive assessment of hepatic fibrosis: Ultrasound-based elastography", section on 'Efficacy of transient elastography'.)

Host factors

Demographic features — Various demographic features have been associated with disease progression in observational studies of individuals with chronic HCV:

- **Sex** – Male sex has been associated with faster fibrosis progression [89]. Among women, menopausal and post-menopausal statuses have been associated with fibrosis progression [90,91].

- **Age** – Acquisition of HCV after age 40 to 55 may be associated with a more rapid progression of liver injury [53,92]. In contrast, infected children appear to have a relatively decreased risk of disease progression [41]. (See "Hepatitis C virus infection in children", section on 'Natural history'.)

- **Race/ethnicity** – Progression may be slower and histology less severe in Black individuals compared with those of other races [63,93-95]. In addition, certain complications of liver disease, particularly hepatocellular carcinoma, are more common in Japan than in the United States [96]; it is not entirely clear whether this is due only to host characteristics, or whether viral differences or the environment might also play a role. (See "Epidemiology and risk factors for hepatocellular carcinoma".)

- **Route of HCV acquisition** – Patients who acquire the disease from a blood transfusion may be at increased risk for disease progression compared with those infected via other modes [28,97]. However, this relationship has not been confirmed in all studies [98].

Comorbidities — Certain comorbidities have been implicated in progression of liver disease in the setting of chronic HCV infection:

- **HIV infection** – Patients co-infected with HIV and HCV have an accelerated rate of progression to cirrhosis.

- **HBV infection** – Liver disease is typically more severe in patients with active HBV and HCV coinfection than either infection alone. (See 'Viral factors' below and "Hepatitis B virus: Clinical manifestations and natural history", section on 'Hepatitis C virus infection'.)

- **Diabetes mellitus and insulin resistance** – Several studies have demonstrated a greater risk of fibrosis progression and cirrhosis in patients with diabetes mellitus and insulin resistance [87,99-101]. This association may be due, in part, to the risk of hepatic steatosis in such patients, which is itself associated with fibrosis progression (see 'Liver histology' above). Among HCV-infected patients who have cirrhosis associated with chronic HCV infection, diabetes mellitus has also been associated with complications such as encephalopathy, bacterial infection, and hepatocellular carcinoma [102].

- **Obesity** – Patients who have a high body mass index and hepatic steatosis are at increased risk for the development of fibrosis [66,87,89,103-106]. (See 'Liver histology' above.)

- **Vitamin D deficiency** – In a meta-analysis of seven studies, a vitamin D level <10 ng/mL was associated with advanced fibrosis [107].

Behavioral factors — Behavioral factors have also been associated with the rate of disease progression:

- Alcohol use has a major negative impact on disease progression. (See 'Alcohol intake' below.)
- Regular coffee consumption has been associated with a lower rate of disease progression, reduced hepatic fibrosis, and lower risk of hepatocellular carcinoma [108-110]. (See "Epidemiology and risk factors for hepatocellular carcinoma", section on 'Lifestyle factors'.)
- Daily use of marijuana has been associated with the development of hepatic steatosis and more rapid fibrosis progression, possibly through stimulation of endogenous, hepatic cannabinoid receptors [111-113].
- Higher levels of dietary cholesterol consumption have been associated with an increased risk of clinical and histologic progression of liver disease [114]. In contrast, statin use has been associated with lower fibrosis progression rate and decreased risk of progression to cirrhosis and hepatic decompensation [115-118].

Effects of host genetic factors on the natural history of chronic HCV infection have also been studied [119-123]. A study involving 128 patients with various stages of HCV related liver disease found a significant relationship between fibrosis stage and profiles of a profibrogenic cytokine transforming growth factor B1 (TGF B1), suggesting that genetic polymorphism of these genes may be an important determinant of the fibrosis progression rate [119]. The host cellular immune response to HCV-specific targets also appears to influence the severity of liver injury; however, its role in progressive liver injury is not clear [120]. Different genes in various HLA subregions also modulate the inflammatory response by complex interaction [121]. Interleukin-28B (IL28B) genotype is a known predictor of how a patient will respond to treatment with peginterferon and ribavirin, but its effect on the progression of fibrosis is unclear. In one study, an IL28B allele that is typically associated with an unfavorable response to treatment was associated with baseline significant fibrosis or rapid progression of fibrosis for non-genotype 1 infections only [122]. Other studies have not supported an association between IL28B genotype and fibrosis progression [89].

Alcohol intake — Heavy alcohol use has been associated with progression of liver disease in patients with chronic HCV infection. As an example, in a meta-analysis of 16 studies that included more than 15,000 HCV-infected patients, heavy alcohol use (>240 to 560 g/week) was associated with a higher risk of cirrhosis (compensated or decompensated) compared with less heavy use (relative risk [RR] 2.33, 95% CI 1.67-3.26) [124]. Similarly, in another seminal study, daily consumption of 50 g or more of alcohol was associated with a 34 percent increase in the

rate of fibrosis progression. A standard drink contains 12 g of alcohol and is equivalent to 360 mL (12 oz) of beer, 150 mL (5 oz) of wine, and 45 mL (1.5 oz) of whiskey or other 80-proof distilled spirits.

It is uncertain whether light or moderate intake of alcohol increases the risk of progression of liver disease in HCV infection, as data are limited and some, but not all [125,126], studies have found an association.

These observations probably explain the epidemiologic reports of a high prevalence of anti-HCV antibodies in patients with alcohol use disorder and either cirrhosis or liver failure [127,128]. Alcohol use is also associated with hepatocellular carcinoma and increased mortality in HCV-infected patients [129,130]. Thus, alcohol intake should be avoided in all patients with chronic HCV infection. (See "Hepatitis C and alcohol".)

Viral factors — The effect of viral factors on disease progression is less certain than host factors. The size of the infectious inoculum (viral dose) does not appear to be important [43]. Data regarding the role of viral genotype and quasispecies in predicting outcome are too contradictory to reach definitive conclusions [53,131-135]. As an example, while some reports have suggested that genotype 1b is overrepresented among patients with cirrhosis and those with hepatocellular carcinoma [136,137], other studies found no such association after adjusting for disease duration or patient age [98,138,139]. This suggests a cohort effect (ie, patients infected with genotype 1b having had disease for longer amounts of time).

Another observation is that the disease may be accelerated in patients who are infected by more than one HCV genotype, suggesting that coinfection may have an additive or synergistic harmful effect [98,139]. Acute exacerbations of chronic HCV infection, the causes of which are unknown, may also be associated with more rapid fibrosis progression. (See 'Acute exacerbation of chronic infection' above.)

Similarly, coinfection with hepatitis B virus (HBV) and HCV may also result in more rapid disease progression [140-142]. The significance of HBV and HCV coinfection may be underestimated since many coinfected patients lack serologic markers of HBV infection. This was illustrated in a study in which 33 percent of 200 HBV surface antigen (HBsAg) negative HCV-infected patients had detectable HBV deoxyribonucleic acid (DNA), in contrast to 14 percent of 50 HCV-uninfected controls with liver disease and negative HBsAg [141]. The reason why some patients with HCV who are infected with HBV lack HBsAg is unknown. While some of these patients have hepatitis B core antibodies, in others, all markers are absent. The lack of HBsAg does not appear to be related to mutations within the gene encoding for the region [141]. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Coinfection with HCV or HDV'.)

Predictive models — Several studies evaluating the risk factors for disease progression have developed multivariate models that attempt to predict outcomes in individual patients [98,143,144].

- Baseline data collected as part of the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial were used to develop predictive models for both clinical and histologic outcomes [143]. The 1050 patients in the HALT-C trial were previous nonresponders to standard interferon therapies who had advanced fibrosis on liver biopsy. Clinical outcomes were defined as an increase in Child-Pugh score to seven or greater, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and liver-related death. The histologic outcome for the study was an increase in Ishak fibrosis score of two or more points (biopsies taken at 1.5 and/or 3.5 years after randomization).

  Factors predictive of clinical outcomes on multivariable analysis were elevated aspartate aminotransferase (AST)/alanine transaminase (ALT) ratio, elevated total bilirubin, low albumin, low platelet count, and increasing Ishak fibrosis score. Factors predictive of histologic progression were increasing body mass index, low platelet count, and hepatic steatosis.

- In another study, clinical and laboratory variables among 247 patients with varying degrees of HCV histologic severity were analyzed [98]. Death from liver failure, the development of hepatocellular carcinoma, and liver transplantation were considered together in the statistical analysis [98]. A history of hepatic decompensation (defined as at least one episode of ascites, jaundice, hepatic encephalopathy, or gastrointestinal bleeding of variceal origin) and the serum albumin concentration were independent predictors of the above outcomes. Patients without a history of decompensation and a serum albumin concentration greater than 4.1 mg/dL (41 g/L) had only a 3 percent chance of developing one of the endpoints within five years versus approximately 6 percent in patients with one of these factors, and 40 percent in patients with both factors.

SPECIAL POPULATIONS

Pregnant women — Relatively few studies have examined the course of HCV infection during pregnancy. The available data are summarized separately. (See "Pregnancy in women with pre-existing chronic liver disease", section on 'Chronic hepatitis C virus' and "Vertical transmission of hepatitis C virus".)

Immunosuppressed hosts — Patients with certain immunocompromising conditions have a more rapid progression of liver disease than those without. This is well established in patients with HIV coinfection and who have received a liver transplant for chronic HCV infection. (See "Hepatitis C virus infection in liver transplant candidates and recipients".)

There are fewer data on the effects of other agents that affect the immune system on the natural history of HCV infection. It appears that such agents do not adversely affect the course of HCV infection in a clinically substantial way, in contrast to their negative effect on hepatitis B virus (HBV) infection.

- **Glucocorticoids** — It is doubtful that a short-course of glucocorticoids would have a major impact on the progression of liver disease. In patients who require long-term steroids, it is reasonable to repeat assessment of liver fibrosis in two to three years to see if progression has occurred. Patients with HCV who are exposed to glucocorticoids experience an increase in HCV viral load, although the effect of such changes on the natural history of HCV is uncertain. The effect of glucocorticoids on aminotransferases is variable, although they tend to decrease [145,146]. In an illustrative study, 10 patients with chronic HCV were given a seven-week course of tapering prednisone [145]. Serum ALT levels decreased in eight patients (from 184 to 84 units/L) and then rebounded in seven after discontinuation. HCV RNA levels increased during therapy (by about one log) and then decreased to pretreatment values within an average of 2.8 weeks (range 1 to 5). By contrast, serum aminotransferases and bilirubin increased in another report in which treatment was continued for 16 weeks [147]. However, there was no significant change in liver histology.

- **Cytotoxic chemotherapy** — Although data are limited, the risk of significant liver dysfunction in HCV-infected patients undergoing chemotherapy is low, although acute increases in the viral load and serum aminotransferases can occur [46,148,149]. Studies on the time to develop cirrhosis among HCV-infected patients who undergo hematopoietic stem cell transplant (HSCT) have not suggested an aggressive fibrosis progression rate, but HCV infection has been associated with an increased non-relapse mortality rate following HSCT [150-152]. (See "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Conventional cytotoxic agents", section on 'Hepatitis C' and "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Hepatitis C virus'.)

- **Tumor necrosis factor-alpha inhibitors** — Data on the effects of TNF-alpha inhibitors on the natural history of chronic HCV infection are limited, but they are generally thought to be minimal. This is discussed elsewhere. (See "Tumor necrosis factor-alpha inhibitors: Bacterial, viral, and fungal infections", section on 'Hepatitis C'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatitis C virus infection".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Hepatitis C (The Basics)")
- Beyond the Basics topics (see "Patient education: Hepatitis C (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Although many patients with chronic hepatitis C virus (HCV) infection are symptomatic, most symptoms are nonspecific and not clearly a result of HCV infection itself. Even if cirrhosis develops, many patients have only nonspecific symptoms. Some patients have extrahepatic findings (such as cryoglobulinemia, renal disease, or specific dermatologic disorders) that are directly related to HCV infection. (See 'Clinical features' above.)
- There is wide variability in serum aminotransferase levels in patients with chronic HCV infection over time. Up to one-third of patients have normal levels. Occasionally, acute increases in the serum aminotransferases can occur during chronic HCV infection without apparent alternate cause. HCV RNA levels generally remain constant during chronic infection with <1 log fluctuations. (See 'Laboratory findings' above.)

- Following acquisition of HCV, 50 to 85 percent of patients remain chronically infected. Of those, approximately 5 to 30 percent develop cirrhosis over the subsequent 20 to 30 years, although slower and faster rates of fibrosis progression have been described. Patients who develop cirrhosis are at further risk for complicating events (such as variceal hemorrhage, ascites, and encephalopathy) and hepatocellular carcinoma, although many patients with compensated cirrhosis remain stable for years. Overall survival is decreased in patients with chronic HCV infection, especially in those who have developed cirrhosis. (See 'Natural history' above.)

- The baseline level of liver fibrosis is an important clinical predictor of further fibrosis progression. Patients with no fibrosis and minimal hepatic inflammation have a very low risk of progressing to cirrhosis. Once an individual has developed advanced fibrosis (ie, bridging fibrosis or METAVIR stage F3), the risk of progression to cirrhosis is approximately 10 percent per year. (See 'Liver histology' above.)

- Host factors that appear to be adversely associated with fibrosis progression in individual HCV-infected patients are older age, male sex, non-Black race, alcohol use, and comorbidities such as obesity or viral coinfection. The impact of viral factors (such as genotype or diversity) is less evident. (See 'Factors associated with disease progression' above.)

- Although elevations in the serum aminotransferase levels have been observed in patients with chronic HCV infection with the use of immunosuppressive medications, it is uncertain whether this affects fibrosis progression. However, certain immunocompromised populations, such as HIV-coinfected and liver transplant patients, have accelerated fibrosis rates. (See 'Immunosuppressed hosts' above.)

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Topic 3672 Version 52.0

GRAPHICS

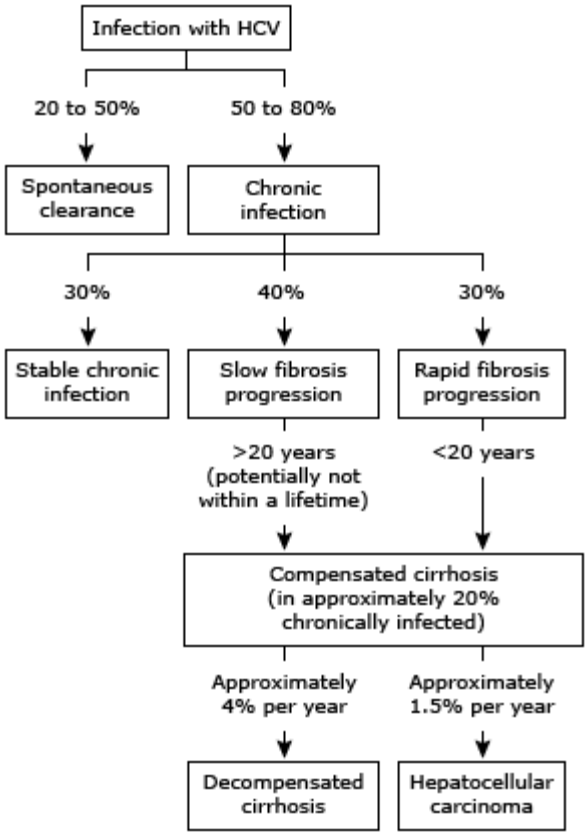
Prevalence of clinical extrahepatic manifestations in 321 patients with chronic HCV infection

	N (percent)
Skin involvement	
Purpura	21 (7)
Raynaud phenomenon	21 (7)
Cutaneous vasculitis	19 (6)
Pruritus	20 (6)
Psoriasis	6 (20)
Porphyria cutanea tarda	3 (1)
Lichen planus	3 (1)
At least one skin manifestation	55 (17)
Rheumatologic involvement	
Arthralgia	60 (19)
Arthritis	6 (2)
Myalgia	31 (2)
Neurologic involvement	
Sensory neuropathy	28 (9)
Motor neuropathy	15 (5)
Miscellaneous	
Sicca syndrome (mouth)	40 (12)
Sicca syndrome (eye)	32 (10)
Hypertension	32 (10)
Uveitis	2 (1)
Overall	
At least one extrahepatic clinical manifestation	122 (38)

Data from: Cacoub P, Renou C, Rosenthal E, et al. Medicine 2000; 79:47.

Graphic 66842 Version 2.0

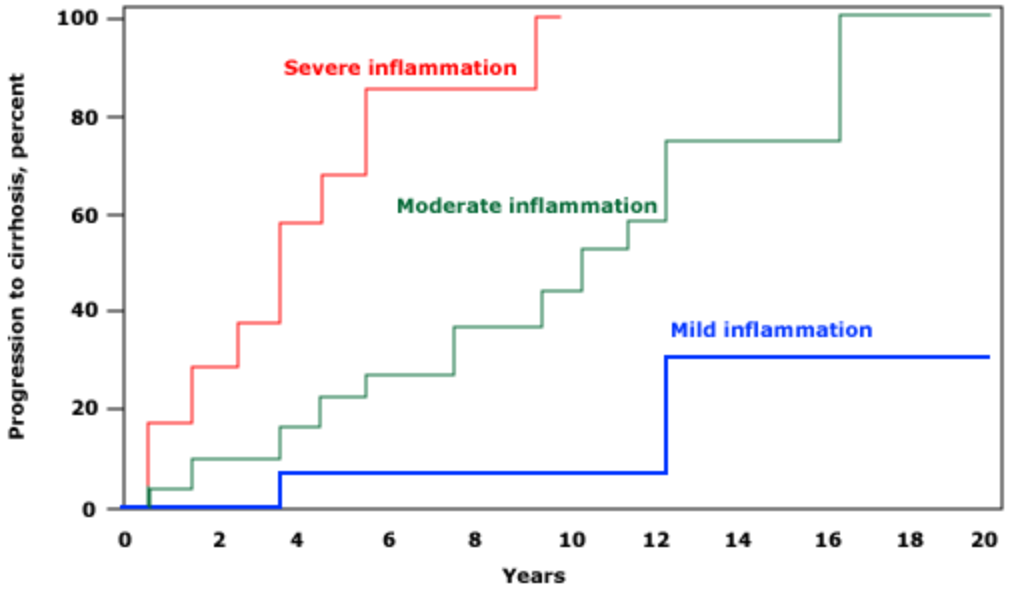
Natural history of hepatitis C virus



The likelihood of chronic infection following acquisition of HCV and the rate of fibrosis progression depend on various host and viral factors. As examples, young women and children are more likely to spontaneously clear HCV infection, and if chronically infected, have relatively slow fibrosis progression rates. Refer to the UpToDate topic on the natural history of HCV infection for further details.

Graphic 99947 Version 2.0

Progression of hepatitis C to cirrhosis according to baseline inflammation on initial liver biopsy



In this study of 70 patients with chronic hepatitis C virus infection, those with mild inflammation (portal inflammation alone or with only focal periportal extension) and no fibrosis on the initial liver biopsy had only a 1.2 percent annual risk of progressing to cirrhosis (blue line). In comparison, patients with moderate chronic hepatitis (periportal inflammation usually involving more than 30 percent of the limiting plate) had a 4.6 percent annual risk of developing cirrhosis (green line), and those with severe inflammation or bridging fibrosis had a high risk of progression (red line); nearly all in the last group developed cirrhosis within ten years.

Data from Yano, M, Kumada, H, Kage, M, et al, Hepatology 1996; 23:1334.

Graphic 72654 Version 1.0

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Sanjiv Chopra, MD, MACP No relevant financial relationship(s) with ineligible companies to disclose. **Adrian M Di Bisceglie, MD** Equity Ownership/Stock Options: Arbutus [Hepatitis B]. Consultant/Advisory Boards: Eiger [Hepatitis D]; HighTide Therapeutics [Primary sclerosing cholangitis, nonalcoholic steatohepatitis]; Ocelot Bio [End stage liver disease]; WCG/ACI [Clinical trial conduct]. All of the relevant financial relationships listed have been mitigated. **Allyson Bloom, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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