

# Course and Outcome of Hepatitis C

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Hepatitis C is a common problem in the United States and abroad. It is currently estimated that there are between 140 million and 170 million people worldwide infected with the hepatitis C virus (HCV), and that nearly 4 million people in the United States have been exposed, almost 3 million of whom persist in carrying the virus. There is reason to believe that this figure may be an underestimate of the true burden in this country.

Although much is known about the course of the acute illness and the long-term sequelae of the virus infection, in-depth study of the acute and chronic disease is difficult for various reasons. The study of acute hepatitis C is complicated by the fact that only a small proportion of infected persons (between 10% and 25%) develop typical symptoms of acute hepatitis so that information on the characteristic biologic manifestations have had to come from prospective studies of high-risk groups, such as transfusion recipients, offering the opportunity to study both recognized and subclinical illness. The study of chronic hepatitis also is made difficult by the fact that onset of acute onset is rarely identified; transition from acute to chronic hepatitis occurs silently, without clinical manifestations; and the chronic hepatitis that ensues may last two to four or more decades without the knowledge of the affected person. Therefore, differing strategies have had to be employed for the study of the natural history of chronic hepatitis C, and these have yielded important but, as yet, incomplete information.

## **Acute Hepatitis C:**

Within an average of one week after initial exposure to the hepatitis C virus (HCV) (2 to 21 days), the virus can be detected in the blood. Biochemical evidence of disease, namely elevation of serum enzymes, especially alanine aminotransferase (ALT), occurs approximately 4 weeks after exposure (14 to 75 days), symptoms (if they occur) develop about 7 weeks after exposure (14 to 150 days), and anti-HCV appears an average of 9 weeks (35 to 150 days) after exposure. Prospective studies indicate that about one-quarter of infected persons develop clinical symptoms; in contrast, persons identified to be infected through routine screen rarely recognize a past acute bout when questioned. In general, 80% to 85% of acutely infected persons fail to clear virus by about 6 months after infection, thus progressing to chronic hepatitis. However, the spontaneous recovery rate appears to be higher (30% to 45%) among people infected at a younger age, especially among younger women.

## **Chronic Hepatitis C:**

The precise timing of initiation of chronic hepatitis is uncertain, but by convention, is defined as the persistence of HCV RNA for at least 6 months after initial infection. Certainly, it appears that if HCV RNA is still detectable one year after infection, it rarely, if ever disappears thereafter. Most, but not all, chronically-infected persons have abnormal aminotransferase levels as evidence of chronic hepatitis. Generally, the value for ALT is higher than that of aspartate aminotransferase (AST), but this ratio often reverses as cirrhosis develops. Other biochemical values are usually normal early in the course of chronic hepatitis but begin to show changes if and when the disease progresses to a state of decompensation. Progression of chronic hepatitis is a consequence of advancing fibrosis, beginning first with periportal fibrosis, advancing in some to bridging fibrosis of increasing severity, culminating in the development of cirrhosis. These individuals are at risk of developing hepatocellular carcinoma (HCC). Indeed, in patients with chronic hepatitis C, HCC rarely develops in the absence of cirrhosis. The rate of development of HCC in persons with cirrhosis is 1 %-4% per year.

For the reasons described above, there has been great difficulty in defining the true natural history of chronic hepatitis C. The primary problem has been the inability to date onset of the disease in most infected person other than by inference. The other obvious problem is the markedly prolonged course of the chronic illness. For these reasons, various strategies have been devised to study the course of chronic hepatitis C, each of which has yielded useful information, although each has had its failings.

The first approach was a series retrospective investigations, tracing persons with identified HCV infection admitted to well-regarded academic centers back to the presumed time of disease onset and then drawing conclusions regarding the presumed course of the illness. The view reached from these studies was that evolution to cirrhosis and ultimately, HCC, was common among patients chronically-infected with hepatitis C. This was an appropriate conclusion based on the collected information, but the validity of the data can be called into question by the fact that patients admitted to these centers mostly had overt liver disease whereas infected persons with minimal disease would not have come to their attention. This is an example of referral bias. A later series of prospective studies described less serious disease, but the usefulness of these studies were compromised by their relatively short duration of follow-up (16 years being the longest). Later, a series of retrospective-prospective cohort studies involving younger people (infants, young women exposed to contaminated Rh immunoglobulin; young injection drug users, young military men) described an even slower rate of evolution of chronic liver disease.

Based on these many and varied studies, it can be concluded that, among older infected persons (over about 40 of years of age), about 20% will progress to cirrhosis by approximately 20 years after first infection. In contrast, persons infected at a younger age, particularly young females, progress far less frequently to the development of cirrhosis, so that at 20 years after initial infection, between 1 % and 5% have developed cirrhosis. What remains unclear is what the course of the disease is in the subsequent two decades. This question has greatest relevance for people infected at a young age because they have many years of life ahead of them. One possibility is that fibrosis progresses at a linear rate. Modeling outcome based on this assumption has led to the conclusion that there will be a doubling of deaths from HCV-related chronic liver disease in the course of the next 10 to 15 years. Another scenario is that progression may increase exponentially, as a consequence of the immune deficit that accompanies the aging process and hence the disease will advance more rapidly. Yet a third scenario is that the rate of fibrosis progression is defined early in the course of infection so that fibrosis may plateau in some people and the disease therefore not advance. There is more yet to be learned about the natural history of hepatitis C.

It is clear, however, that there are a number of factors that may have an impact on the rate of progression. The rate of progression appears not to be defined by characteristics of the virus, but rather by host-related and certain extraneous factors. Important among these is age at the time of infection and perhaps the aging process itself; gender, women appearing to advance at a slower rate than men; and race, whites appearing to advance at a faster rate than African Americans. Co-infection with other viruses, such as the human immunodeficiency virus (HIV) and the hepatitis B virus (HBV) also have a strong influence on the rate of progression. Other comorbidities that may affect the advancement of liver disease include the presence of iron overload, especially as a consequence of hemochromatosis, non-alcoholic steatohepatitis (NASH), and schistosomiasis, common in the past among the Egyptian population. There are also accumulating data to suggest that there may be genetic influences on the rate of progression. And finally in regard to host factors, the mode of disease expression has definite implications, whether as cause or effect. Thus, infected persons who have normal aminotransferase levels generally have milder disease than do those with raised enzyme levels. That is not to say that persons with normal enzymes may not have severe bridging fibrosis or cirrhosis. Such lesions are found in individuals with normal enzymes but far less frequently than among those with elevated enzymes. With regard to extraneous factors, one of the most important contributors to fibrosis progression is the co-existence of chronic alcoholism. Numerous reports identify chronic alcoholism as a major factor in disease progression. What is not clear, however, is what level of alcoholism plays an unquestionably additive role, but more importantly, below what daily level of alcohol ingestion will no harm ensue. A few studies suggest the heavy smoking may also contribute to fibrosis progression, but this factor needs confirmation in better-designed studies. Finally, it is conceivable that some environmental contaminants may have an additive effect, this conclusion based on the strong evidence that HCC is a far more common sequel to chronic hepatitis C among persons infected in Japan than among Japanese born in other countries or among those infected in the United States.

There are too few studies to describe the long-term sequelae of chronic hepatitis C in persons with chronic renal disease but presumably the course is more complicated and far worse than it is in persons without renal disease.

## **References**

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