The epidemiology and natural history of hepatitis C virus infection

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■ ABSTRACT

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States. HCV infection is generally benign in its acute stage but tends to become chronic in more than 70% of patients, at which stage it can induce liver cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Approximately 2.7 million Americans are estimated to have chronic HCV infection. Although the incidence of HCV infection is believed to be falling, the prevalence of HCV-related liver disease is rising. Better identification of risk factors for HCV transmission and improved understanding of the infection's natural history should refine measures for preventing the spread of infection and preventing complications in those infected.

The story of hepatitis C began a little more than 2 decades ago, when researchers transmitted non-A, non-B hepatitis from patients with transfusion-associated hepatitis to chimpanzees, demonstrating that the disease resulted from a transmissible agent. A major breakthrough came in 1989 with the cloning of the hepatitis C virus (HCV) genome by Choo et al.[1] Shortly after the discovery of HCV, it became apparent that this newly identified virus is the principal causal agent for non-A, non-B hepatitis. The rapid development of sensitive serologic assays for antibodies to HCV led to a large reduction in the incidence of transfusion-associated hepatitis, but it raised many important questions about the epidemiology, natural history, and socioeconomic burden of this viral infection.

In the first years after the discovery of HCV, its primary role in post-transfusion hepatitis and its tendency to induce persistent infection after exposure were widely documented. These early years generated considerable debate about whether HCV was associated with significant morbidity or mortality in infected patients. Compelling evidence, however, linked HCV infection to liver failure and hepatocellular carcinoma (HCC) and was followed by a series of well-designed studies that suggested an increase in liver-related mortality among patients with chronic HCV infection.[2–4] We now firmly recognize that HCV infection is associated with substantial morbidity and mortality and that it clearly represents a global public health challenge.

■ EPIDEMIOLOGY OF HCV INFECTION IN THE UNITED STATES

Worldwide, nearly 170 million people, or about 3% of the global population, are estimated to be infected with HCV.[5] Although the US infection rate is lower, HCV infection has reached epidemic proportions in the United States and is now the most common chronic blood-borne infection in the nation.[5]

Most people with chronic HCV infection are not aware that they are infected, owing to the symptomless onset of acute HCV infection and the insidious progression of chronic infection. Infected persons serve as a source of transmission to others and are at increased risk for chronic liver disease and other HCV-related chronic systemic disorders. The lack of a prophylactic vaccine or a universally effective therapy has made prevention extremely important in this chronic infection. Identification of infected persons and of risk factors associated with acquiring HCV may allow us to develop strategies to reduce the incidence of HCV infection and control the resulting epidemic.

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Prevalence and incidence of HCV infection

Prevalence. The most accepted figures on the prevalence of HCV infection in the United States are from the Third National Health and Nutrition Examination Survey (NHANES III), a national survey of noninstitutionalized civilians conducted from 1988 through 1994.[6] Because NHANES III was a population-based household survey, it probably underestimated the prevalence of HCV infection, given the high prevalence of antibodies to HCV in incarcerated, homeless, and institutionalized persons.

Based on findings among 21,000 survey participants tested for antibodies to HCV, the NHANES III researchers estimated that 1.8% of the US population, or approximately 3.9 million Americans, were infected with HCV and that 74% of this group, or approximately 2.7 million Americans, had chronic infection associated with HCV viremia (detectable serum HCV RNA).[6]

NHANES III also delineated racial differences in the prevalence of HCV infection. The prevalence of antibodies to HCV among African Americans (non-Hispanic blacks in NHANES III) was more than twice that among non-Hispanic whites (3.2% vs 1.5%); likewise, the rate of viremia among those with antibodies to HCV was higher in African Americans than in non-Hispanic whites (86% vs 68%). The highest observed prevalence of HCV infection, 9.8%, was among African American men aged 40 to 49 years.[6]

The prevalence of HCV infection is much higher among some specific populations, including patients seen at Veterans Affairs clinics (18% to 40%), prison inmates (40% to 54%), and homeless persons.[7–9]

Incidence. Estimates of the incidence of HCV infection are more difficult to generate and less likely to be accurate, given the subclinical presentation of acute HCV infection. However, data from the US Centers for Disease Control and Prevention (CDC) suggest that the annual incidence of HCV infection fell from an estimated 230,000 new cases per year in the late 1980s to approximately 35,000 new cases per year in the 1990s.[5,10] The decline has been attributed mainly to the screening of blood donors for HCV antibodies and to safer needle-use practices among injection-drug users.

Although the incidence of HCV infection may be decreasing, the prevalence of liver disease associated with chronic HCV infection, including liver failure and HCC, is rising.[10] As a result, HCV-related disease is the leading indication for liver transplantation in the United States.[5]

Methods of HCV transmission

Direct blood or fluid exposure. Direct percutaneous or permucosal exposure to infectious blood or bodily fluid is the most apparent and documented mode of HCV transmission.[11] Direct exposure includes transfusion of HCV-contaminated blood products, parenteral drug use, accidental needle injuries in health care workers, and receipt of an organ transplant from an infected donor.

Sexual activity. The risk of acquiring HCV from sexual activity remains controversial.[12] While there is sufficient evidence to support the conclusion that sexual transmission of HCV occurs, the efficiency of this route of transmission appears to be low. The estimated risk of sexual transmission of HCV is 0% to 0.6% per year for those in long-term monogamous relationships, and 1% per year for those with multiple sexual partners.[12] No change in sexual practices is recommended for people in long-term monogamous relationships, whereas those with multiple or short-term sexual partners should use barrier methods of protection against sexually transmitted diseases (STDs).

Higher rates of seropositivity for antibodies to HCV have been reported among prostitutes, homosexual men, and heterosexual men attending STD clinics.[13–15] Among persons engaged in high-risk sexual behaviors, those with human immunodeficiency virus (HIV) coinfection were more likely to be positive for antibodies to HCV than those who were HIV-negative, even after controlling for factors that may influence sexual transmission.[16] These data suggest that certain sexual behaviors and HIV coinfection are factors that increase the transmission of HCV by sexual contact.

Perinatal transmission. The prevalence of HCV in otherwise healthy children is not known but is much lower than that in adults. Several investigators have reported a relatively high efficiency of vertical mother-to-infant transmission of HCV in mothers coinfected with HIV.[17] However, mother-to-infant transmission is not efficient (< 6% risk of transmission) in mothers who are HIV-negative.[17]

Because of their recognized exposure, children born to an HCV-infected woman should be tested for infection. Testing for antibodies to HCV should not be performed before age 15 months to 18 months since these antibodies may be transmitted passively through the placenta in the absence of

Injection-drug use is the transmission route for most cases of HCV infection
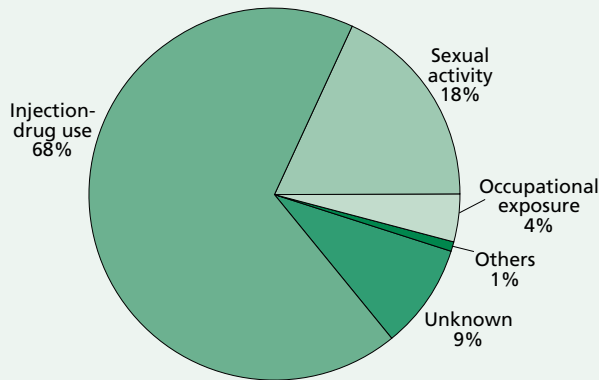
FIGURE 1. Sources of HCV infection in the United States, based on Centers for Disease Control and Prevention data obtained from 1995 to 2000.

HCV infection. Testing for HCV RNA can be done earlier, during the first few weeks of life, to identify infants with active infection, and should be repeated to confirm the results, whether positive or negative. Because HCV is not transmitted through casual contact, there is no reason to exclude HCV-infected children, including those with active infection, from day care or from play at school.[11]

Occupational exposure. Like sexual and vertical transmission of HCV, occupational transmission has been well documented but is thought to be rare. Prospective studies in health care workers after occupational exposure have documented transmission only after needlestick injuries with contaminated needles. All medical centers should establish policies for counseling health care workers after percutaneous or permucosal exposure (needlestick injuries and blood splashes), testing these workers for HCV, and providing appropriate follow-up care.[11]

Transmission of HCV from infected health care workers to patients is so rare as to justify publication of individual case reports.[18]

Potential risk factors. Several potential risk factors for acquiring HCV, including tattooing, acupuncture, ear piercing, incarceration, military service, and foreign travel, have been evaluated in case-control studies of acute infection and were found not to be associated with HCV transmission.[6,11] Data from the CDC indicate that injection-drug use accounts for most newly acquired cases of HCV in the United States today, followed by sexu-

al transmission **(Figure 1)**. In only 9% of cases is a source of transmission not identified.

■ **NATURAL HISTORY OF HCV INFECTION AND PREDICTORS OF PROGRESSION**

Acute infection and chronicity
Acute hepatitis C (detection of HCV RNA in the blood after initial exposure to the virus) is generally a benign disease. In the transfusion setting, where acute onset of HCV infection has been best documented, 70% to 80% of cases are anicteric (not associated with jaundice) and asymptomatic.[19] Acute HCV infection can be severe, but fulminant liver failure associated with acute infection is extremely rare.[20] Given the rarity of fulminant disease and the benign nature of acute HCV infection, the significance of HCV infection lies in its tendency to become persistent and induce chronic liver disease.

The rate of chronicity after acute HCV infection is not well established but is believed to exceed 70%.[21] Several factors that correlate with a lower rate of chronicity have been identified, including younger age at infection, female sex, nonblack race, and development of jaundice during acute infection.[21] Patients with immunologic deficits are at an increased risk of developing chronic HCV infection.

Complications of chronic infection vary
Several long-term complications may develop in patients with chronic HCV infection, including cirrhosis, end-stage liver disease, and HCC, although there is significant biologic variation among infected patients. This variation became apparent in studies of the natural history of HCV infection. Tong et al[22] showed in a retrospective US study that the mean time from HCV exposure at transfusion to the diagnosis of clinical cirrhosis was approximately 21 years, while the mean time to diagnosis of HCC was 28 years. Severe complications such as cirrhosis and HCC developed over a relatively short period (10 to 15 years) in some patients, whereas other patients had no complications despite longer periods of infection. It has been estimated that 20% of patients with chronic HCV infection develop cirrhosis after 20 years of infection.[2]

These biologic variations in disease outcomes suggest that cofactors might contribute to the outcome of chronic HCV infection. The French team of Poynard et al[23] conducted a multicenter trial that included more than 2,200 HCV-infected patients. Of nine potential cofactors evaluated, three inde-

pendent factors were associated with an increased rate of fibrosis progression:

- Age greater than 40 years at the time of HCV infection
- Daily consumption of more than 50 g of alcohol
- Male sex.

Among factors not associated with more advanced liver disease were HCV genotype and serum HCV RNA level.[23]

Other cofactors have been associated with more severe HCV-related liver disease in other studies, including race (black patients are less likely to progress to cirrhosis), coinfection with other viruses, such as hepatitis B virus and HIV, and genetic influences.[24–26]

Hepatocellular carcinoma

The development of HCC in HCV-infected patients is particularly significant, given the number of patients with chronic HCV infection and the poor outcome of HCC. The risk of HCC is estimated to be up to 17 times greater in HCV-infected patients than in their HCV-negative counterparts.[27] Underlying cirrhosis appears to be a prerequisite for the development of HCC in patients with chronic HCV infection. Among patients in whom cirrhosis is established, the estimated annual incidence of HCC is 1% to 4%.[28,29]

In light of these findings, routine screening for HCC is currently recommended for patients with HCV infection; patients should be screened at 6-month intervals using serum alpha fetoprotein level and hepatic ultrasound examination.[30] Antiviral therapy with interferon may reduce the risk of HCC in patients with chronic HCV infection, although this remains an issue of debate.[27]

Extrahepatic manifestations

Another dilemma in the natural history of chronic HCV infection is the development of extrahepatic manifestations. **Table 1** lists some of the most common of these.[31–37] It remains to be shown whether these conditions are directly caused by HCV infection or result from underlying liver disease.

HCV-related cryoglobulinemia is the most frequent extrahepatic manifestation of HCV and has been reported in up to 50% of patients. Symptomatic cryoglobulinemia is uncommon, however, occurring in less than 1% of patients. Symptomatic cryoglobulinemia presents clinically with manifestations of vasculitis, including skin rash, renal dysfunction, neuropathy, and fatigue. Cryoglobulin-

TABLE 1
Extrahepatic manifestations of chronic HCV infection

Essential mixed cryoglobulinemia

Porphyria cutanea tarda

Membranoproliferative glomerulonephritis

Diabetes mellitus

Autoimmune thyroiditis

Sjögren syndrome

Lichen planus

Lymphoma

emia typically responds to interferon therapy for HCV infection, but relapse is common once therapy is stopped in those who do not achieve sustained viral eradication.

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