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Evolving Epidemiology of Hepatitis C Virus in the United States

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Abstract

The impact of hepatitis C virus (HCV) infection on health and medical care in the United States is a major problem for infectious disease physicians. Although the incidence of HCV infection has declined markedly in the past 2 decades, chronic infection in 3 million or more residents now accounts for more disease and death in the United States than does human immunodeficiency virus (HIV)/AIDS. Current trends in the epidemiology of HCV infection include an apparent increase in young, often suburban heroin injection drug users who initiate use with oral prescription opioid drugs; infections in nonhospital healthcare (clinic) settings; and sexual transmission among HIV-infected persons. Infectious disease physicians will increasingly have the responsibility of diagnosing and treating HCV patients. An understanding of how these patients were infected is important for determining whom to screen and treat.

The first descriptions of the epidemiology of hepatitis C virus (HCV) infection date well before both the actual identification of the virus in 1989 [1] and the US Food and Drug Administration's approval of tests to detect antibody to hepatitis C virus in 1992. "Non-A, non-B hepatitis" was identified as a cause of chronic liver disease among transfusion recipients in studies during the 1970s in the United States [2] and abroad [3]. Since then, hepatitis C in this country has gone from an unknown and untreatable infection, mainly identified when transmitted through receipt of blood or hemodialysis, to an identifiable and curable—but underappreciated—infection today. In this article, we review trends in incidence, prevalence, mortality, and mode of transmission of HCV infection in the United States.

INCIDENCE OF ACUTE, SYMPTOMATIC HCV INFECTION

The lack of a simple test to determine the meaning of a positive HCV-antibody test remains one of the greatest obstacles to HCV infection epidemiology, diagnosis, and determination of which patients need treatment. A positive HCV-antibody test can imply either chronic HCV (about 80%) or resolved HCV (about 20%), or some small fraction of new, acute HCV

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infections. States voluntarily report persons with acute HCV disease (cases) in accordance with the case definitions of the Council of State and Territorial Epidemiologists/Centers for Disease Control and Prevention (CDC) (Table 1). The case definition for acute HCV—which is different from the diagnostic criteria a clinician would use—is complicated and hard to fulfill (see Table 1). The surveillance case definition is purposely kept specific to ensure that only definite acute cases are reported to the CDC. Reports require both clinical and laboratory criteria, so asymptomatic acute cases are not reportable and usually not identified by passive surveillance. Because it is simpler to "confirm" an acute case who has developed jaundice and has a positive HCV-antibody test, almost 70% of cases reported to CDC have jaundice [4]. More problematic for health departments is the volume of pieces of information, that is, laboratory tests, physician reports, or other documents that require processing to identify new cases [5].

According to CDC surveillance, the incidence rate of HCV infection peaked in 1992 at 2.4 (confirmed and reported) cases per 100 000 population. Since then, rates have declined by 88% to 0.3 cases per 100 000 population in 2009 [4]. Declines have been most dramatic among persons aged 30–39 years (92%; from 5.8 cases per 100 000 population in 1992 to 0.5 cases per 100 000 population in 2009) (Figure 1). In 2009, after accounting for asymptomatic, undetected, and unreported infections, there were an estimated 16 000 new infections in the United States [4]. Data on genotypes are sparse, but the harder-to-treat HCV genotypes 1a and 1b appear to continue to account for about 73% of all infections, and genotypes 2 and 3 (easier to treat) account for almost all of the remainder [6].

PREVALENCE OF CHRONIC INFECTION

To monitor seroprevalence of chronic infection (defined as positive for HCV-RNA) in the US household population, the CDC uses data from the National Health and Nutrition Examination Survey (NHANES). During 1988–2002, an estimated 2.4–3.9 million persons had chronic infection [7, 8]. Seroprevalence of antibodies is highest among adults aged 40–49 years (4.3%), males (2.1%), and black non-Hispanics (3.0%). Models generated from NHANES data indicate that a cohort of new infections during the 1980s resulted in a higher prevalence of chronic infection decades later among persons born from 1940 to 1965 [8]. The aging of this cohort has resulted in ever-increasing healthcare utilization [9].

MORBIDITY

Despite sparse data and follow-up, it is generally accepted that for 25%–30% of those infected, 20–30 years will elapse between infection and cirrhosis [10]. Of those with cirrhosis, ≥25% will develop end-stage liver disease or hepatocellular carcinoma resulting in death if liver transplantation is not performed. However, precirrhotic infection is not benign, and many or most HCV-infected patients suffer fatigue, arthralgias, and emotional depression; many if not most have reduced physical and social functioning. HCV infection has now also been associated with steatosis, insulin resistance and diabetes [11], renal disease, and certain types of lymphomas; other organ systems that may be involved include the central nervous system, lymphatic system, eyes, blood vessels, and peripheral nerves

[12]. All of these conditions lead to increased hospitalization of HCV patients, 15% per year [13].

MORTALITY

Trends in deaths are available from the national multiple-cause mortality data that the National Center for Health Statistics prepares from about 2.4 million deaths each year. Ly and colleagues recently reported that during 1999–2007 [14] the average annual age-adjusted mortality rate of deaths in which HCV was an underlying or contributing cause increased by 0.18 deaths per 100 000 persons per year; for comparison, similar deaths related to human immunodeficiency virus (HIV) declined by 0.21 deaths per 100 000 persons per year. By 2007, HCV was more often listed as an underlying or contributing cause of death than HIV ([14]; Figure 2). However, only 40%–50% of decedents who have HCV will have been diagnosed at the time of death [15], whereas at least 80% of decedents with HIV infection have been diagnosed before death [16]. Thus, based on these proportions, the disparity between HCV- and HIV-related deaths must be even greater.

EPIDEMIOLOGY

It is important to remember that HCV has long been recognized as essentially a parenterally transmitted infection [7]. The main difficulty in determining exceptions to this rule is interpreting a wide array of studies in which risk factors or risk behaviors, such as injection drug use and sharing of needles, may not be adequately distinguished from risk markers, such as having many sex partners or having tattoos. These markers are often classic confounding variables—for example, having multiple sex partners and tattoos—that may be associated with (unacknowledged) injection drug use and are not actual sources of infection.

Receipt of Infected Blood

Before universal (HCV antibody) screening of blood donors for HCV in 1992, many non-A, non-B hepatitis infections were transmitted through blood, tissue, and organ donation. Although this source of infection accounts for many of the estimated 3 million Americans in the baby boom generation with chronic HCV infection [8], this epidemiologic dynamic has shifted, as effective interview and laboratory screening of blood donors has, over the past 20 years, removed it as an infection source. It is now estimated that only 1 in 1 million blood transfusions may transmit HCV [17]. Currently, most concern is about whether to add HCV nucleic acid testing (NAT) in screening of blood, tissue, and organ donors to tighten the “window period” between infection and detection from about 60 days (HCV antibody test positivity) to 3–5 days (NAT testing) [18].

Injection Drug Use

As receipt of blood products, tissues, and organs has been safe for 2 decades, the importance of injection drug users (IDUs) in HCV transmission has comparably increased in developed countries [4, 19]. The incidence of HCV infection among IDUs can be as high as 40 per 100 person-years, especially among new injectors [20–23]. National viral hepatitis surveillance from 2009 confirms that 241 of 432 acute HCV cases (56%) who responded to the question,

"Have you used injection drugs in the past 6 months?" answered "yes" [4]. However, using surveillance data to estimate what proportion of new cases can be ascribed to HCV infection is problematic. Many acutely HCV-infected persons are not interviewed or will not answer questions about risk. Additionally, few physicians ask about [24], and few patients wish to admit to [25], injection drug use. Worse, when a respondent does not admit to injection drug use but does respond to positively to questions about sexual contacts, HCV infection may be inappropriately ascribed to sexual behavior [26]. Thus, given that 56% of those acute cases interviewed answer affirmatively to injection drug use, this behavior must account for the great majority of new cases of HCV infection. While IDUs are at the center of the current hepatitis C epidemic, they remain exceedingly difficult to locate and investigate and provide interventions to. Currently, we are aware of only a relatively few local studies of IDUs that are funded by the US federal government, so some conclusions must be deduced from sparse data. Several mysteries bedevil us.

The first mystery is why acute HCV infections in all age and risk groups have declined so dramatically in the past 20 years (Figure 1). In the absence of a vaccine, and before an antibody test allowed screening of blood and blood products (1992), there was nonetheless the beginning of a decline in acute HCV cases in all age groups. We may never know the answer to why new HCV infections have plummeted, but ancillary behavior related to the HIV/AIDS epidemic has been posited as one reasonable explanation, as IDUs began using sterile needles or entered drug treatment [27] in response to the fear of acquiring AIDS. Another is that the number of active IDUs has declined as many entered treatment and discontinued drug use, shifted from injection to noninjection practices, or simply died from overdose, infection, or other risks attendant to drug use.

Another mystery relates to transmission dynamics: the numbers and rates do not add up. Most studies show very high prevalence of HCV infection among older IDUs (≥80% in IDUs aged ≥50 years), and whereas this prevalence may have declined in recent years [28], HCV antibody prevalence rates in IDUs aged 18–40 years has remained at ≤35% in recent years [29]. In fact, the most recent studies of IDUs aged ≤40 years indicate that only 25% are infected [30]. Moreover, the risk of HCV infection does not increase in a steady incremental fashion for IDUs. Most IDUs apparently acquire HCV infection during their first years of injection [23, 31]. So why does HCV seroprevalence jump from the 20%–30% range among persons aged ≤40 years to >70% among those aged ≥50 years? Studies of IDUs are few, underfunded, and small in scope, so some of this mystery may be simply explained by insufficient statistical power and largely unmeasured changes in injection drug use over the past 20 years. Are IDUs without HCV infection better able to stop injecting drugs and thereby not be included in surveys of older IDUs? We simply do not know.

Finally, another mystery relates to the impact of intervention programs. A few studies have indicated that IDUs who attend needle and syringe exchange programs are less likely to acquire HCV infection or, as more often studied, HIV [32, 33]. A few studies also indicate the beneficial effects of drug treatment programs. However, although it is hard to argue with the progress seen in Figure 1, some may question whether this derives from public health intervention programs for IDUs [34, 35].

Also undermining any comfort from the declining incidence curves shown in Figure 1 is the recognition recently of a whole new cohort of young IDUs who are acquiring HCV infection. These “new” IDUs have been recently seen in Massachusetts [36], upstate New York [37], Wisconsin, and, less frequently, Indiana. These new injectors share a number of qualities not seen in previous cohorts of IDUs: they are typically aged ≤24 years, white, and nonminority, usually nonurban, and likely to have used oral prescription opiod congeners before using heroin [30]. In-depth interviews of some of these young IDUs show that they typically initiate substance (alcohol, marijuana) abuse at very young ages (mean age, 13 years), transition to oral opiod use (oxycodone [Oxycontin]) by mean age 17 years, then start using cheaper and more available injected heroin by age 18 years [38].

Transmission in Healthcare Settings

It has long been appreciated that hepatitis C—formerly known as non-A, non B hepatitis—is a special problem in hemodialysis centers [39, 40]. These centers have taken many strides to prevent HCV (or hepatitis B virus [HBV]) infection by “cohorting” or isolating viral hepatitis–infected patients in special rooms or sections of the dialysis center; more scrupulously adhering to infection-control principles, such as nonreuse of needles or sharing of medication vials; regularly screening for HCV (and HBV and HIV); and providing vaccination for hepatitis A virus and HBV for patients with HCV infection [39]. As a result, clusters of infections in dialysis units have been decreasingly detected.

Unfortunately, not all healthcare facility settings have taken similar steps. An outbreak investigation in Las Vegas, Nevada, in 2008 [41] stimulated a review of similar outbreaks known to the CDC, and without special effort, 16 investigated outbreaks of HCV infection from 1998 to 2008 were enumerated [42]. These outbreaks identified 275 incident HCV infections and were almost always associated with the reuse of syringes resulting in contamination of medicine vials or intravenous fluids subsequently used for other patients. While 6 outbreaks occurred in hemodialysis centers—none in dialysis clinics since 2006—11 were in a wide variety of nonhospital healthcare settings: private physicians’ offices, pain remediation clinics, an anesthesiologist’s office, alternative medicine or chelation therapy clinics, and nuclear imaging facilities, as well as the endoscopy clinics that spurred interest [42].

The detection of so many HCV clusters and cases occurring in places where patients should never be infected is of special concern. If one considers that ≥80% of acutely HCV-infected adults have no symptoms, that only some of those who are symptomatic may come to the attention of a doctor and then a health department, and that beleaguered and underfunded local and state health departments may not have the ability to link ≥2 cases to a health facility, the fact that 1–2 such clusters have been detected each year is remarkable [43]. Then, even if detected, the investigatory team may be met by legal and bureaucratic resistance from the implicated facility, and records may be poorly kept such that follow-up of potentially exposed patients is very difficult [41]. In sum, these detected outbreaks must be the tip of a much larger problem.

Sexual Transmission

As indicated at the outset of this section, sexual transmission of HCV is thought to account for a very small fraction of new or old cases of HCV infection. It is accepted by most researchers in this field that an HCV-infected partner in an otherwise healthy heterosexual pair does not transmit to the susceptible partner [44, 45]. In fact, 3 prospective cohort studies of such discordant partner-pairs have failed to detect a single transmission in >9000 person-years of observation and an estimated 750 000 sexual encounters [44]. However, there are important exceptions.

In recent years, acute HCV infection among HIV-infected men who have sex with men ("serosorted" by their HIV infection status) have been increasingly detected in Europe and the United States [46–49] (also please see article by Taylor and Mayer that more fully treats this issue). Less appreciated are data from the Women's Interagency HIV Study, which also suggest that women with HIV, too, are at increased risk of acquiring HCV infection compared with HIV-uninfected women [50]. HIV infection should be recognized as a condition that increases one's risk of HCV infection and reinforces the need for HIV-infected persons to use condoms when having sex even with another (known) HIV-infected partner.

Other special circumstances also deserve an asterisk. If HCV infection risk increases with the number of sex partners, but not the number of sex acts with a given infected partner [44], this suggests that transmission may occur between 2 people as an all-or-none phenomenon, at the time of their first sex act(s). Thus, given the more frequent likelihood of matching with an HCV-transmitting partner, it makes intuitive sense that those with many lifetime sex partners have an increased risk of acquiring HCV infection, even if the risk is small. Similarly, factors that disrupt genital mucosal integrity such as genital ulcerative diseases (herpes, syphilis) or rough sex may facilitate the transmission of HCV [44, 45].

Still, all things considered, we should be cautious when attributing HCV transmission to sexual activity, given the many potentially confounding factors.

Tattoos, Piercing

To date, the CDC is unaware of any outbreak of HCV infection in the United States associated with a commercial, licensed, regulated tattoo or piercing parlor. After many years of observation, these regulated settings seem to be safe in terms of their practices [51, 52].

Here, too, exceptions should be noted. HCV infections in Australia and the United States have possibly or probably occurred in men who received homemade tattoos in prison [53, 54]. Receiving noncommercial tattoos—that is, those applied in by friends or in settings such as prisons, homes, or other unregulated and unsterile conditions—might transmit HCV [52].

The Challenge Of Prevalent HCV Infections

Although epidemiology and public health traditionally focus on the prevention of acute infection, chronic HCV infection needs attention, as approximately 3 million US residents—and some would say more [55]—may be infected with HCV. The forthcoming impact on

public health, disease burden, and infectious disease professionals should not be underestimated. As indicated earlier, ≥65% of these infections and 73% of deaths are among persons in the baby boom generation, now aged 47–65 years, and HCV deaths overall now demonstrably outstrip deaths from HIV/AIDS (Figure 2) [14].

Because “secondary prevention” of disease and death in these chronically infected persons is important, issues of “secondary epidemiology” need to be developed. One large issue is to ensure that more HCV-infected persons—of whom only about half know they are infected [15]—are diagnosed and successfully linked to care (see Smith et al article in this issue [56]). In this sense, traditional surveillance and epidemiology for HCV infection blur into diagnosis and care and will require broad collaboration among public health departments, private practitioners, hospitals, and other clinical facilities.

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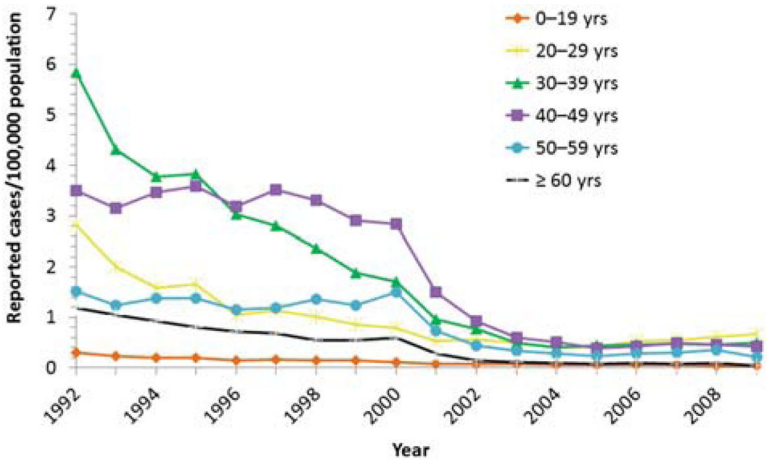

Figure 1.

Reported acute hepatitis C virus (HCV) cases by age group, United States, 1992–2009. Estimated HCV infections are thought to be about 20 times the number of cases reported through the largely passive national surveillance system [4]. (Until 1995, acute hepatitis C was reported as acute hepatitis non-A, non-B.) Source: National Notifiable Diseases Surveillance System.

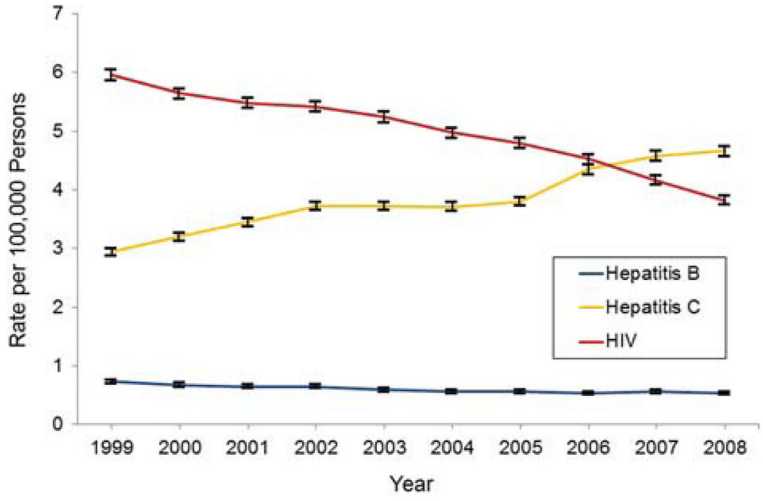

Figure 2.

Annual age-adjusted rates of mortality and 95% confidence intervals of hepatitis B virus, hepatitis C virus (HCV), and human immunodeficiency virus listed as a cause of death in the United States, 1999–2008. Approximately 73% of all HCV-related deaths were in persons aged 45–64 years. [14]. Abbreviation: HIV, human immunodeficiency virus.

Table 1

2012 Council of State and Territorial Epidemiologists' Case Definitions for Hepatitis C

	Past or Present (2012)	**Acute (2012)**
Clinical	None required	Discrete onset of sign/symptoms AND
		Jaundice OR ALT > 400 IU/L
		OR
		None if seroconversion <6 months
Laboratory	Anti-HCV positive with a signal-to-cutoff ratio predictive of true positive	Anti-HCV positive with a signal-to-cutoff ratio predictive of true positive
	OR	OR
	HCV RIBA positive	HCV RIBA positive
	OR	OR
	NAT for HCV RNA (qualitative, quantitative, or genotype)	NAT for HCV RNA (qualitative, quantitative, or genotype)
		AND (if done)
		IgM anti-HAV negative;
		IgM anti-HBc negative

Abbreviations: ALT, alanine aminotransferase; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HCV, hepatitis C virus; IgM, immunoglobulin M; NAT, nucleic acid testing; RIBA, recombinant immunoblot assay.