MAJOR ARTICLE

# Acute Hepatitis C in a Contemporary US Cohort: Modes of Acquisition and Factors Influencing Viral Clearance

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***Background.*** Acute hepatitis C virus (HCV) infection is often asymptomatic; thus, its epidemiology and natural history are difficult to define.

***Methods.*** Acute HCV infection was identified on the basis of HCV seroconversion within 1 year ($n = 45$), new anti-HCV seropositivity with clinical acute hepatitis ($n = 21$), or HCV strain sequencing after an iatrogenic exposure ($n = 1$). Risk factors were assessed with a baseline questionnaire, and participants were followed up prospectively with serial measurement of viral loads.

***Results.*** Of 67 persons with acute HCV infection, most were asymptomatic (64%) and injection drug users (66%). Thirteen had an unknown mode of transmission; of these, 11 reported high-risk sexual behavior. Ten acquired acute HCV infection within 3 months of an iatrogenic exposure; 3 had confirmed iatrogenic infection, and 4 had no other risk factors identified. The spontaneous viral clearance rate after 6 months of infection was 18% (95% confidence interval, 11%–31%). The rate of viral clearance varied significantly by sex (34% vs. 3% for women vs. men; $P < .001$).

***Conclusions.*** High-risk sexual or iatrogenic exposures may be important contemporary risk factors for HCV infection. The spontaneous viral clearance rate (18%) in this contemporary study was similar to that reported for past studies of transfusion-associated HCV infection. Women were more likely to clear acute HCV infection than men.

Epidemiologic and natural history studies of acute hepatitis C virus (HCV) infection are hampered by the difficulty in recognizing asymptomatic acquisition, and acute HCV cohorts enrolled on the basis of symptomatic infection at diagnosis do not represent the entire spectrum of disease. Furthermore, most prospective studies defining the natural history of HCV infection have followed persons with transfusion-acquired infection [1]. However, such infections are now rare, because effective blood product screening has been implemented [2]. Prospective natural history data from contemporary cohorts of HCV-infected patients are needed to define HCV risk factors and the rate of spontaneous viral clearance after acute infection.

We conducted a multicenter study of acute HCV infection. Although we enrolled all persons who had documented acute HCV infection, we focused recruitment on sites likely to identify asymptomatic infection through serial screening, such as blood banks and a research site for injection drug use (IDU). We present epidemiologic data and clinical characteristics of this cohort, as well as factors influencing spontaneous viral clearance in acute HCV infection.

## METHODS

***Patients.*** Patients with acute HCV were recruited from academic medical centers (Seattle, Pittsburgh, and Portland), blood banks (Seattle, Memphis, and Los Angeles), and an IDU research site (Seattle). This study was

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approved by the institutional review boards of all participating institutions. Informed consent was obtained from all participants.

Three methods were used to identify patients with acute HCV infection: (1) a positive HCV antibody or HCV RNA polymerase chain reaction (PCR) assay result in a participant with a documented negative anti-HCV test result within the past year; (2) a positive anti-HCV assay result in a participant with clinical hepatitis, detectable serum HCV RNA, a serum alanine aminotransferase (ALT) level >10 times the upper limit of normal, and negative results of tests for hepatitis B surface antigen and hepatitis A IgM antibody; or (3) in 1 case, comparison of the viral strain from a patella tendon recipient with that of the cadaveric donor [3, 4]. Diagnoses of symptomatic acute hepatitis C were made after patients sought medical attention for symptoms, including nausea, anorexia, abdominal pain, malaise, fever, and jaundice. Diagnoses were made by physicians specializing in hepatology or infectious diseases after evaluation of the patient's clinical presentation and laboratory data.

A 35-item baseline risk factor questionnaire was administered. Risk factors for acute HCV infection were defined hierarchically. IDU was designated as the mode of infection in participants reporting any history of IDU. In participants without a history of IDU, iatrogenic exposure was confirmed in 3 cases and was considered likely if participants reported a medical or dental procedure within 3 months of the estimated date of infection. The remaining participants without any of these risk factors were considered to have unknown mode of infection. Participants were followed prospectively with serial HCV RNA measurements; the frequency of blood samplings varied between each center.

Iatrogenic infection was considered confirmed in 3 participants. The first was a nurse who had documented HCV seroconversion and symptomatic illness after a needlestick exposure from an HCV-infected patient [5]. Two participants were infected after receiving a patella tendon transplant from an HCV-infected cadaveric donor [4]. Both of these infections were confirmed by comparing the viral strain from the recipients with that of the donor. One of these patella tendon recipients developed symptomatic illness. The second participant had HCV viremia without symptomatic illness or documented seroconversion and thus was included in this study on the basis of the molecular epidemiologic evidence alone.

For asymptomatic participants, the midpoint between the last negative antibody test result and the first positive antibody or HCV RNA test result (whichever was earlier) was used to estimate the date of acquisition. For participants who reported symptoms, the acquisition date was estimated as 6 weeks before the onset of symptoms [6]. For the 3 participants with confirmed iatrogenic exposures, the acquisition date was defined as the date of exposure.

***Laboratory methods.*** Serum samples were tested for anti-HCV, ALT, and total bilirubin levels at the local laboratories. The HCV RNA load was measured by using an HCV RNA bDNA assay (Versant 3.0; Bayer Diagnostics), with a lower limit of detection of 615 IU/mL, or by PCR, with a lower limit of detection of 60 IU/mL. Samples negative by the bDNA assay were tested by using an HCV qualitative transcription-mediated amplification RNA assay (Versant; Bayer Diagnostics), with a lower limit of detection of 50 IU/mL. Serum samples were considered undetectable for HCV RNA if they were negative by either the PCR assay or the HCV qualitative RNA assay.

Genotype was determined at baseline by using the INNO-LiPA HCV II assay (Bayer Diagnostics) or a real-time PCR assay (Abbott Diagnostics). In participants who developed recurrent viremia after providing a sample with undetectable HCV RNA, genotyping of the recurring strain was performed. Reinfection was considered to have occurred if the recurring strain was found to be of a different HCV genotype compared with baseline [7].

***Statistical analysis.*** Our criteria for viral clearance required 2 consecutive serum samples with undetectable HCV RNA. The date of viral clearance was defined as the midpoint between the first of 2 consecutive undetectable samples and either the last sample with detectable HCV RNA [8] or the estimated acquisition date, in the event that the first sample collected had an undetectable viral load. Transient viral clearance was defined as recurrence with the same HCV genotype after 2 consecutive undetectable serum samples.

Participants failing to clear HCV demonstrated 1 of the 3 following viral load patterns. Participants who had detectable virus at every time point were considered to have persistent viremia [8]. Participants who had a single sample with undetectable HCV RNA among a series of positive serum samples with the same genotype were considered to have intermittent viremia [8]. Finally, participants who had a single undetectable viral load as their last measurement were not considered to have cleared the infection during follow-up and were censored at the time of the last sample.

Group comparisons involving categorical variables used Fisher's exact test. Kruskal-Wallis tests were used for 3-group comparisons of continuous variables, and where significant differences were found, further testing between 2 groups was performed with Mann-Whitney *U* tests.

Survival analysis methods, including Kaplan-Meier curves, log-rank tests, and Cox regression models, were used to estimate the time from acquisition to viral clearance, to determine the cumulative incidence of clearance at 6 months after acquisition, and to identify factors associated with the rate of viral clearance. Participants were censored at the time of treatment initiation (11 participants after a median pretreatment follow-up time of 160 days) or reinfection (1 participant). Participants who did not clear virus were censored on the last date of HCV RNA measurement. The proportional hazards assumption was assessed by

**Table 1. Demographic characteristics and main risk factors for acute hepatitis C virus infection.**

| Characteristic or exposure | Total ($n$ = 67) | IDU ($n$ = 44) | Iatrogenic ($n$ = 10) | Unknown ($n$ = 13) | $P$[a] |
|---|---|---|---|---|---|
| Men | 35 (52) | 24 (55) | 4 (40) | 7 (54) | .72 |
| Age,[b] median (range), years | 31 (17–82) | 28 (17–50) | 52 (17–82) | 44 (17–48) | <.001 |
| Race | | | | | .26 |
| White | 56 (84) | 38 (86) | 8 (80) | 10 (77) | |
| Black | 5 (7) | 2 (5) | 0 (0) | 3 (23) | |
| Asian or Pacific Islander | 2 (3) | 1 (2) | 1 (10) | 0 (0) | |
| Latin American | 3 (4) | 2 (5) | 1 (10) | 0 (0) | |
| Native American | 1 (1) | 1 (2) | 0 (0) | 0 (0) | |
| Education | | | | | .28 |
| Less than 12th grade | 13 (19) | 7 (16) | 1 (10) | 5 (38) | |
| High school diploma or GED | 22 (33) | 17 (39) | 2 (20) | 3 (23) | |
| More than high school diploma | 32 (48) | 20 (45) | 7 (70) | 5 (38) | |
| Marital status | | | | | .09 |
| Married | 25 (37) | 15 (34) | 7 (70) | 3 (23) | |
| Single, never married | 26 (39) | 20 (45) | 2 (20) | 4 (31) | |
| Other | 16 (24) | 9 (20) | 1 (10) | 6 (46) | |
| IDU, ever | 44 (66) | 44 (100) | 0 (0) | 0 (0) | NT |
| Blood transfusion in past 12 months | 0 (0) | 0 (0) | 0 (0) | 0 (0) | NT |
| Medical or dental procedure within 3 months of estimated date of infection | 15 (22) | 5 (11) | 10 (100) | 0 (0) | NT |
| Occupational needlestick in past 12 months | 1 (1) | 0 (0) | 1 (10) | 0 (0) | NT |

**NOTE.** Data are no. (%) of participants, unless otherwise indicated. IDU, injection drug use; GED, General Educational Development; NT, not tested.

[a] Statistical testing compared participants across all 3 groups. Group comparisons involving categorical variables were performed with Fisher's exact test; Kruskal-Wallis tests were used for 3-group comparisons of continuous variables.

[b] For further 2-group comparisons with Mann-Whitney $U$ tests of age, $P$ = .04 when the group with unknown mode of transmission was compared with the iatrogenic group, and $P$ = .002 when the unknown group was compared with the IDU group.

testing for nonzero slope in the Schoenfeld residuals as a function of analysis time.

Sensitivity analyses were used to explore the effect of estimating alternate acquisition dates representing the opposite extremes for symptomatic (60 days before symptom onset) [6] and asymptomatic participants (7 weeks before the first positive antibody test result or 1 week before the first positive HCV RNA test result) [9]. All analyses were performed using Stata statistical software (version 9.2; Statacorp).

## RESULTS

***Demographic characteristics and modes of infection.*** Sixty-seven persons with acute HCV infection were identified (table 1). The median age was 31 years (range, 17–82 years), most participants were white (84%), and men (52%) and women (48%) were almost equally represented. The most likely risk factor was IDU in 44 participants and iatrogenic exposure in 10 participants. In 13 participants, a risk factor was not identified. No participant reported a blood transfusion in the year before acute HCV infection. These 3 defined risk groups were similar for all demographic factors except for age; those with an unknown exposure mode were significantly younger than participants with iatrogenic exposure ($P$ = .04) and were significantly older than participants with a history of IDU ($P$ = .002).

Persons with unknown modes of HCV infection reported potential risk factors such as recent cocaine use, getting a tattoo in the past year (3 participants), or having an HCV-infected household member (1 participant) (figure 1). Risky sexual behaviors, including sex with a HCV-infected partner, exchange of sex for money, having had >6 lifetime sex partners, initiating sexual activity at <15 years of age, a history of sex with an injection drug user, or sexual activity with a partner of the same sex were common among these participants. When markers of risky sexual behavior were combined into a single variable, participants in the unknown category were significantly more likely to have reported at least 1 of these markers than participants in the iatrogenic category (85% vs. 20%; $P$ = .003).

Ten participants with acute HCV infection had no history of IDU but did have iatrogenic exposure that was either confirmed as the source of HCV infection ($n$ = 3) or occurred within 3 months of the estimated infection date ($n$ = 7) (table 2). The time from iatrogenic exposure to symptoms ranged from 13 to 75 days, consistent with the reported interval between exposure and symptomatic infection [10–13].

One of the participants with a confirmed iatrogenic case, a nurse, developed acute infection after an accidental needlestick from a patient with HCV infection. Two participants who re-

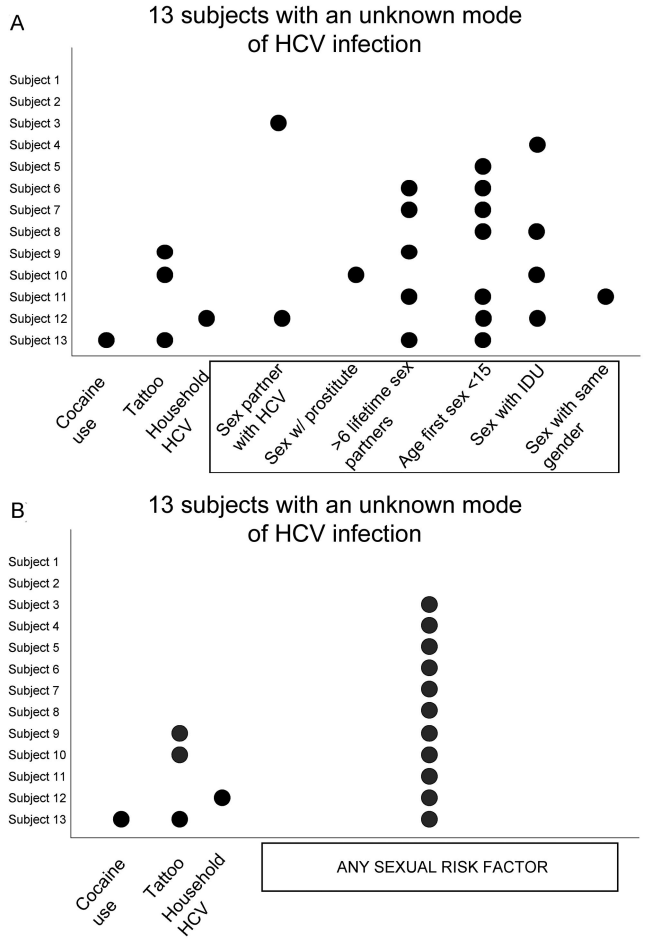


**Figure 1.** High prevalence of sexual risk factors for hepatitis C virus (HCV) acquisition in participants with an unknown mode of acquisition. When sexual risk factors, including a sex partner with hepatitis C, a history of sex with a prostitute, more than 6 lifetime sex partners, sexual debut at <15 years of age, a same-sex partner, or a history of sex with an injection drug user (IDU) *(A),* were combined into a single category designated "any sexual risk factor" *(B),* 11 (85%) of 13 participants with an unknown mode of acquisition reported a sexual risk factor.

ceived patellar tendon transplants had confirmed iatrogenic infections from a cadaveric donor, who was anti-HCV negative but had detectable virus in serum at the time of death [4]. Of the remaining participants with iatrogenic exposures, 3 had other potential risk factors for HCV, whereas 4 did not (table 2).

***Clinical, biochemical, and virologic characteristics of acute HCV infection.*** As shown in table 3, 45 persons (67%) met the case definition for acute HCV infection by documented seroconversion, whereas 21 (31%) were identified after the development of clinical hepatitis. Including 3 participants who had both documented seroconversion and clinical hepatitis, a total of 24 participants (36%) reported symptoms consistent with acute HCV infection. The median ALT and bilirubin levels at enrollment for all participants were 471 (range, 13–2884) IU/L and 1.1 (range, 0.5–28.7) mg/dL, respectively. Genotype 1 HCV infection was present in 42 infected individuals (63%).

***Patterns of viremia and incidence of spontaneous viral clearance.*** During follow-up, participants provided a median of 4 HCV RNA samples each (range, 1–10 samples), with a median of 60 days between samples (range, 1–686 days). The median number of follow-up days from acquisition to the last HCV RNA measurement was 333 days (range, 59–835 days).

Figure 2 shows patterns of serum HCV RNA after acquisition for a subset of patients. Of the 67 total participants, 52 (78%) failed to meet the criteria for viral clearance during follow-up, with 47 being persistently viremic (figure 2*A*–2*C*, representative), 2 being intermittently viremic (figure 2*D* and 2*E*), 2 with a single undetectable sample at the last measurement available, and 1 censored after 224 days, when genotyping revealed a genotype switch from genotype 2b at baseline to genotype 3 at day 281 (figure 2*F*).

Fifteen participants (22%) demonstrated spontaneous HCV RNA clearance during follow-up (figure 2*G*–2*I,* representative). The cumulative incidence of viral clearance at 6 months after acquisition was 18% (95% confidence interval [CI], 11%–31%), with the estimated time to clearance ranging from 32 to 364 days. One of 15 participants demonstrated transient clearance (figure 2*J*). Sensitivity analysis reclassifying this participant as failing to clear viremia did not change the findings of this study.

***Predictors of spontaneous viral clearance.*** Women cleared HCV at a significantly faster rate than men (figure 3*A*). By 6 months after acquisition, 34% (95% CI, 20%–54%) of women had cleared HCV, compared with only 3% (95% CI, 0.5%–20%) of men (hazard ratio [HR], 8.55 [95% CI, 1.92–37.99] (table 3). This effect of sex on the viral clearance rate persisted after adjustment for age and symptoms on presentation (adjusted HR, 6.42 [95% CI, 1.29–32.07]).

We examined age, sex, and the presence of symptoms as potential correlates of viral clearance in a multivariate Cox proportional hazards model. Symptoms at presentation were associated with faster rates of viral clearance univariately (HR, 3.04 [95% CI, 1.08–8.56]) (table 4 and figure 3*B*), but this association did not remain significant once we also adjusted for age and sex (adjusted HR, 1.49 [95% CI, 0.47–4.79]), nor was it significant in sensitivity analyses addressing the different methods used to define date of acquisition in the symptomatic and asymptomatic group (HR, 2.63 [95% CI, 0.93–7.40]). Since women comprised 71% of those presenting with symptoms and only 35% of those without symptoms, it seems likely that the unadjusted difference in viral clearance rates by presence of symptoms was partially due to sex imbalances between the 2 groups.

We further examined the effects of both symptoms and sex on viral clearance rate (figure 3*C*). A Kaplan-Meier analysis including both sex and symptoms (figure 3*C*), suggested that the presence of symptoms during acute HCV infection may have a greater impact on viral clearance in men than in women. When an interaction between sex and symptoms was included in our Cox regression model, the HR for HCV clearance for symptoms

**Table 2. Characteristics of participants with potential iatrogenic exposures to hepatitis C virus (HCV) within 3 months of the estimated date of infection.**

| Age, years | Sex | Procedure | Sexual risk factors | Other potential risk factor[a] | Time from procedure to symptoms, days |
|---|---|---|---|---|---|
| 49 | Male | Patellar tendontransplantation[b] | None | None | Asymptomatic |
| 52 | Female | Patellar tendontransplantation[b] | >6lifetime sexpartners | None | 28 |
| 53 | Female | Needlestick (nurse)[b] | None | None | 36 |
| 17 | Male | Appendectomy | None | Householdmember withHCV | 28 |
| 36 | Female | Breast augmentation | None | None | 43 |
| 37 | Female | Dentalprocedures,dilation and curettage | SexwithHCV-infected injection druguser | Householdmember withHCV | 75 |
| 55 | Male | Intravenouscatheter placement | None | None | Asymptomatic |
| 56 | Female | Ventral hernia repair | None | Householdmember withHCV | 66 |
| 58 | Male | Colonoscopy | None | None | Asymptomatic |
| 82 | Female | Colonoscopy | None | None | 13 |

[a] Risk factors include household member with HCV infection or history of intranasal cocaine use.

[b] These 3 participants had confirmed iatrogenic infection. One nurse was infected after a needlestick and was followed up prospectively until seroconversion to anti-HCV positive status. Two participants who each received a patellar tendon transplant from the same donor had a viral strain matching that from the cadaveric donor, who was HCV RNA positive but anti-HCV negative at the time of patellar tendon harvest.

versus no symptoms was 4.56 (95% CI, 0.29–73.07) among men and 1.44 (95% CI, 0.47–4.44) among women, although this difference was not statistically significant ($P = .45$ for the interaction). However, we have too few participants to address adequately the combined effect of sex and symptoms on HCV clearance. We did not find any significant associations between

**Table 3. Clinical parameters at time of presentation, by risk group.**

| Characteristic | Total ($n = 67$) | IDU ($n = 44$) | Iatrogenic ($n = 10$) | Unknown ($n = 13$) |
|---|---|---|---|---|
| How participant met case definition[a] | | | | |
| Seroconversion | 45 (67) | 36 (82) | 3 (30) | 6 (46) |
| Clinical hepatitis | 21 (31) | 8 (18) | 6 (60) | 7 (54) |
| Confirmed exposure | 1 (1) | 0 (0) | 1 (10) | 0 (0) |
| How participant was identified | | | | |
| IDU site | 32 (48) | 32 (73) | 0 (0) | 0 (0) |
| Blood donation | 10 (15) | 2 (5) | 2 (20) | 6 (46) |
| Parenteral contact | 2 (3) | 0 (0) | 2 (20) | 0 (0) |
| Symptoms | 23 (34) | 10 (23) | 6 (60) | 7 (54) |
| Clinical hepatitis[b] | 24 (36) | 10 (23) | 7 (70) | 7 (54) |
| Genotype | | | | |
| Type 1[c] | 42 (63) | 26 (59) | 8 (80) | 8 (62) |
| Type 2 | 9 (13) | 7 (16) | 1 (10) | 1 (8) |
| Type 3 | 7 (10) | 6 (14) | 0 (0) | 1 (8) |
| Unable to genotype | 9 (13) | 5 (11) | 1 (10) | 3 (23) |
| Bilirubin level,[d] median (range), mg/dL | 1.1 (0.5–28.7) | 1 (0.5–13.5) | 1.1 (0.5–8.3) | 5.0 (0.5–28.7) |
| ALT level,[d] median (range), IU/L | 471 (13–2884) | 201 (13–2884) | 576 (44–1890) | 819 (68–2056) |

**NOTE.** Data are no. (%) of participants, unless otherwise indicated. IDU, injection drug use; ALT, alanine aminotransferase.

[a] Seroconversion was defined as a positive hepatitis C virus (HCV) antibody or HCV RNA polymerase chain reaction assay result in a participant with a documented negative result of an anti-HCV test within the past year. Clinical hepatitis was defined as symptoms including nausea, anorexia, abdominal pain, malaise, fever, and jaundice together with detectable serum HCV RNA, serum ALT levels >10 times the upper limit of normal, and negative results of tests for hepatitis B surface antigen and hepatitis A IgM antibody. One patellar tendon recipient without documented seroconversion or clinical hepatitis was included after he was found to be infected with an HCV strain that matched that of a cadaveric donor. Patellar tendon surgery had occurred in the year before study enrollment.

[b] Three participants with documented seroconversion were symptomatic.

[c] Type 1 includes 2 type 1/2 mixed genotype infections and 1 type 1a/3a mixed genotype infection.

[d] Biliribubin and ALT values are based on the first measurement within 6 months of acquisition; 8 participants were missing baseline laboratory data.

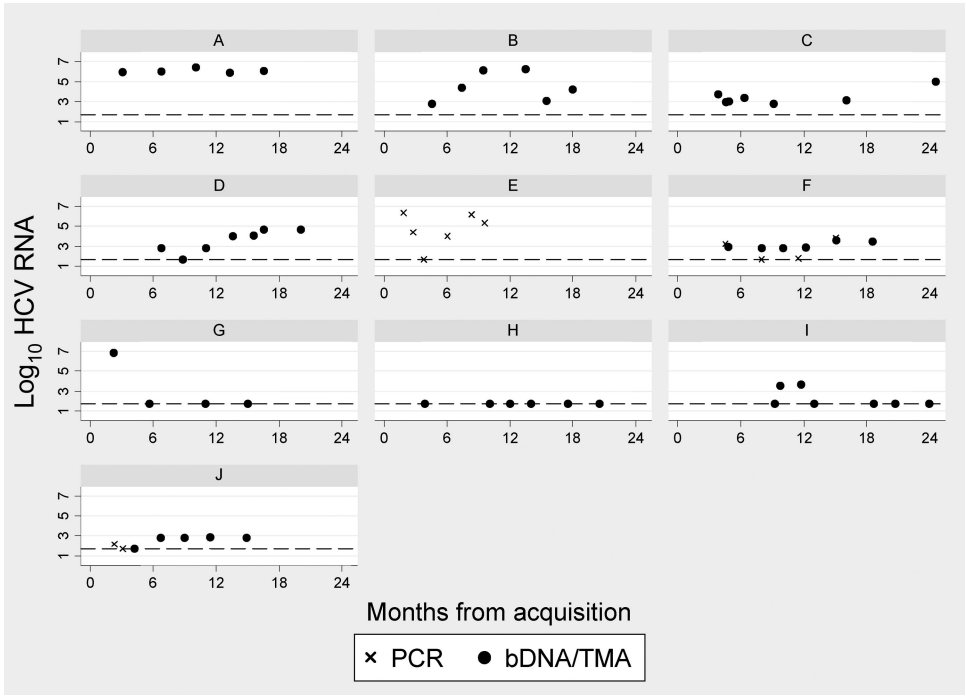


**Figure 2.** Examples of patterns of hepatitis C virus (HCV) RNA over time since acquisition. Dashed reference lines represent the limit of detection; undetectable samples are plotted along these lines. Samples that were undetectable by the bDNA assay but that were detectable by the qualitative transcription-mediated amplification (TMA) RNA assay are shown at a viral load of 615 IU/mL. *A–C,* Examples of persistent viremia. *D* and *E,* Two patients who had a single undetectable sample in a series of samples with the same genotype of detectable HCV RNA. *F,* Reinfection with a new genotype. Reinfection was detected at day 281 in this participant, who thus was censored at the previous sample, on day 224. *G* and *I,* Examples of patients with sustained viral clearance. *J,* HCV RNA measurements for the person with transient viral clearance. PCR, polymerase chain reaction.

rate of viral clearance and age, race, genotype, or likely mode of transmission, and we did not find evidence for violation of the proportional hazards assumption.

## DISCUSSION

Our study presents epidemiologic and clinical data from 67 persons with acute HCV infection enrolled in the years 2003–2005 from multiple clinical centers. To our knowledge, this is the largest such group of patients reported from the United States. Our study provides insights into modes of HCV infection following the virtual elimination of transfusion-associated HCV infection and demonstrates the spontaneous viral clearance rate in this contemporary cohort of persons with acute HCV infection. While most other recent studies of acute HCV infection have been limited by size and study group homogeneity, the heterogeneous nature of our cohort allowed us the opportunity to explore factors associated with spontaneous viral clearance.

Although IDU has long been recognized as a risk factor for HCV infection [14], other modes of transmission are less well defined. Despite a high HCV prevalence in sexually transmitted disease clinic populations [15] and documented transmission during risky sexual behaviors in men who have sex with men [16], the risk of sexual transmission in discordant partners appears to be negligible [17–19]. In our study, as in an Italian study of acute HCV infection [20], high-risk sexual behaviors were common in individuals without IDU or iatrogenic exposures, suggesting that sexual acquisition was a potential route of infection. Furthermore, the significantly older age in the non-IDU group compared with the IDU group supports the concept that HCV is transmitted less efficiently through nonparenteral routes compared with parenteral routes. Of interest, the prevalence of high-risk sexual behaviors in those with an unknown mode of transmission was similar to that in injection drug users, in whom sexual high-risk behavior is common [21]. Thus, persons at risk for HCV infection may be "risk-taking" individuals, even if they do not inject drugs. As such, clinical settings such as sexually transmitted diseases clinics may be appropriate venues for HCV preventive efforts.

We also found that medical procedures were potential risk factors for acute HCV infection. In the past several years, increasing numbers of iatrogenic acute HCV infections have been reported in the United States and elsewhere [20, 22–25]. A recent article from Israel reported that iatrogenically transmitted HCV accounted for 65% of acute HCV infections studied [26]. Iatrogenic HCV has been associated with the use of multidose saline solutions in the United States [22–24], and with gastrointestinal and urologic procedures in Europe [20, 27]. A challenge in con-

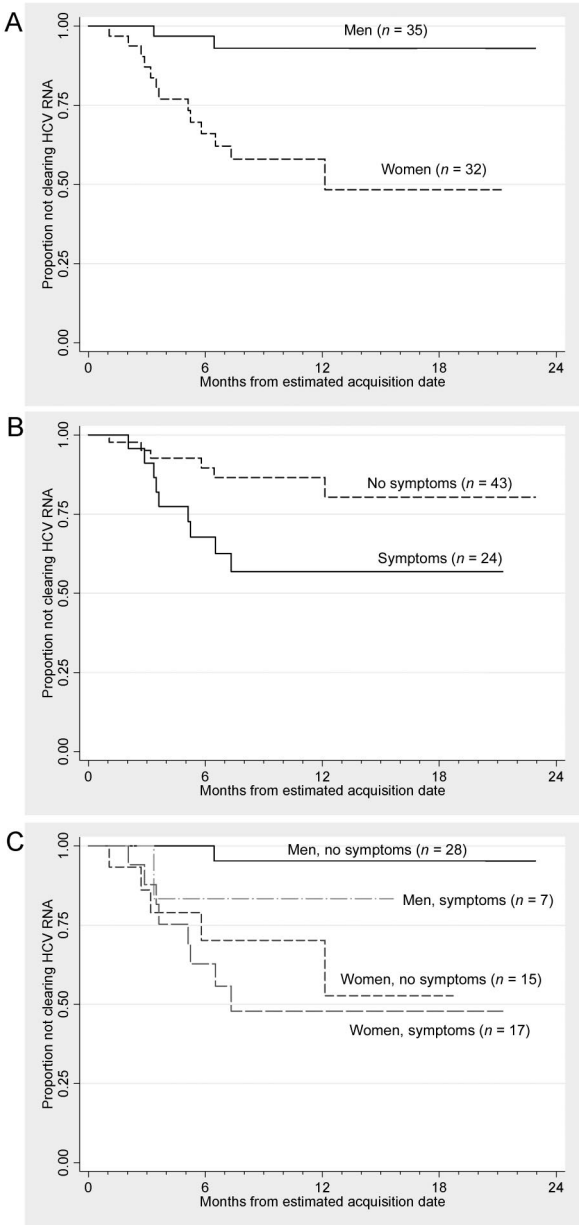


**Figure 3.** Kaplan-Meier curves of time to viral clearance by sex and symptoms. *A,* Sex. Women demonstrated faster rates of viral clearance than men. *B,* Reported symptoms at presentation. Participants who reported symptoms showed faster rates of viral clearance than participants reporting no symptoms. *C,* Sex and symptoms combined. Symptoms during acute hepatitis C infection may have a greater impact on viral clearance in men than in women. HCV, hepatitis C virus.

firming iatrogenic HCV transmission is that many acute infections are asymptomatic, so that an outbreak may not be recognized and a public health response is often lacking.

We report an 18% spontaneous viral clearance rate at 6 months in our study. In comparison, a recent meta-analysis of 31 acute HCV studies including 675 persons demonstrated a pooled rate of 26% [28]. Spontaneous viral clearance rates varied from 0% to 80%, depending on the characteristics of the study population. Two recent European studies that reported high spontaneous clearance rates (35% and 58%) included many symptomatic persons and a high prevalence of genotype 2 or 3 infection [20, 29]. In contrast, in a recent US study, the spontaneous clearance rate was 20%, no patients were symptomatic, and only 15% of patients had genotype 2 or 3 infection [30].

A distinctive contribution of our study is that the comparatively large sample size and heterogeneous population allowed exploration of the relative importance of sex and symptoms at presentation on the spontaneous viral clearance rate in a single group of acutely infected individuals. Genotype was not associated with viral clearance in our study, although in a Taiwanese study [31], clearance rates were higher for those with genotype 2 or 3 compared with genotype 1 infection in univariate but not in multivariate analysis. In another study, symptomatic disease and female sex were univariately associated with spontaneous viral clearance, but small sample size precluded multivariate analysis [29]. In the pooled analysis described above, women ($P = .00001$) and studies focusing on symptomatic infections ($P = .001$) demonstrated the highest viral clearance rates [28]. Results from our study demonstrate that in univariate analysis both female sex and symptomatic acute hepatitis C were associated with faster rates of spontaneous viral clearance, but in multivariate analysis only female sex remained predictive of spontaneous viral clearance. While definitive results from subgroup analyses are precluded by sample size, our data suggest that women with symptomatic acute HCV infection may be most likely to clear virus spontaneously.

Our study has several limitations. First, for most participants the date of acquisition was estimated on the basis of serologic and virologic data, since exposures could have occurred over several months. Second, because we used genotyping and not sequencing to rule out reinfection before describing intermittent viremia or transient viral clearance, reinfection with the same genotype would not have been identified, thus potentially delaying censoring during Kaplan-Meier analysis. However, the results of sensitivity analysis did not suggest that the impact of such limitations would be substantial. We lacked molecular epidemiologic data confirming possible iatrogenic infections in 7 of 10 individuals who had exposures to medical equipment 3 months before acute HCV infection. Similarly, we lacked molecular documentation of sexual transmission among participants reporting high-risk sexual behavior.

Our finding that female sex and symptomatic hepatitis are associated with faster rates of spontaneous viral clearance during acute HCV infection suggests that clinicians may elect to observe women with symptomatic acute hepatitis C for spontaneous viral clearance. In contrast, clinicians caring for men with new asymptomatic HCV infection may choose to initiate antiviral therapy early in the course of infection once it becomes apparent that the serum viral load is not declining.

**Table 4. Unadjusted hazard ratios (HRs) from Cox proportional hazards models for time to viral clearance of hepatitis C virus (HCV) RNA.**

| Covariate | Participants, no. | Cumulative incidence of clearance at 6 months, % (95% CI)[a] | Unadjusted HR (95% CI) | *P* | Adjusted HR (95% CI)[b] | *P* |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| Male | 35 | 3 (0.5–20) | 1.00 | <.001 | 1.00 | .01 |
| Female | 32 | 34 (20–54) | 8.55 (1.92–37.99) | | 6.42 (1.29–32.07) | |
| Age | | | | | | |
| 17–25 years | 17 | 29 (12–61) | 1.00 | .14 | 1.00 | .34 |
| 26–30 years | 16 | 14 (4–46) | 0.32 (0.06–1.58) | | 0.53 (0.10–2.73) | |
| 31–45 years | 19 | 6 (0.8–33) | 0.22 (0.05–1.11) | | 0.28 (0.06–1.42) | |
| 46–82 years | 15 | 27 (11–56) | 0.84 (0.25–2.75) | | 0.94 (0.28–3.19) | |
| Race | | | | | | |
| White | 56 | 17 (9–31) | 1.00 | .89 | | |
| Other | 11 | 24 (6–67) | 0.90 (0.20–3.99) | | | |
| Genotype | | | | | | |
| Type 1[c] | 42 | 11 (4–26) | 1.00 | .56 | | |
| Type 2 or 3 | 16 | 6 (0.9–37) | 0.53 (0.06–4.44) | | | |
| Symptomatic | | | | | | |
| No | 43 | 10 (4–25) | 1.00 | .03 | 1.00 | .49 |
| Yes | 24 | 32 (17–56) | 3.04 (1.08–8.56) | | 1.49 (0.47–4.79) | |
| Mode of transmission | | | | | | |
| Injection drug use | 44 | 13 (6–28) | 1.00 | .62 | | |
| Iatrogenic | 10 | 22 (6–64) | 1.69 (0.45–6.36) | | | |
| Unknown | 13 | 32 (13–64) | 1.67 (0.50–5.54) | | | |

**NOTE.** CI, confidence interval.

[a] Survival analysis methods included Kaplan-Meier curves, log-rank tests, and Cox regression models.

[b] Adjusted for age, sex, and symptoms at presentation.

[c] Type 1 includes 2 patients with type 1/2 mixed genotype infection and 1 patient with type 1a/3a mixed genotype infection; 9 patients whose infections were unable to be genotyped were excluded.

Understanding the biological basis for our described association between female sex and spontaneous HCV clearance may lead to improved insights into the immunologic response during acute HCV infection. This association has been noted in a longitudinal study [29] and a pooled analysis [28] described above, as well as in several cross-sectional studies [32–34]. Superior immunologic responses in women compared with men have been described in other infections [35, 36], and the higher prevalence of autoimmune diseases in women has long been recognized [37]. In addition, women with chronic hepatitis B and C have lower rates of progression to liver-related death and hepatocellular carcinoma than men [38, 39]. Studies of the immune response to acute HCV infection should be performed in cohorts including both men and women in order to explore potential biological mechanisms for the sex associations described in this study.

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