MAJOR ARTICLE

Risk Factors and Outcome among a Large Patient Cohort with Community-Acquired Acute Hepatitis C in Italy

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Background. The epidemiology of acute hepatitis C has changed during the past decade in Western countries. Acute HCV infection has a high rate of chronicity, but it is unclear when patients with acute infection should be treated.

Methods. To evaluate current sources of hepatitis C virus (HCV) transmission in Italy and to assess the rate of and factors associated with chronic infection, we enrolled 214 consecutive patients with newly acquired hepatitis C during 1999–2004. The patients were from 12 health care centers throughout the country, and they were followed up for a mean ($\pm$ SD) period of 14 $\pm$ 15.8 months. Biochemical liver tests were performed, and HCV RNA levels were monitored.

Results. A total of 146 patients (68%) had symptomatic disease. The most common risk factors for acquiring hepatitis C that were reported were intravenous drug use and medical procedures. The proportion of subjects with spontaneous resolution of infection was 36%. The average timespan from disease onset to HCV RNA clearance was 71 days (range, 27–173 days). In fact, 58 (80%) of 73 patients with self-limiting hepatitis experienced HCV RNA clearance within 3 months of disease onset. Multiple logistic regression analyses showed that none of the variables considered (including asymptomatic disease) were associated with increased risk of developing chronic hepatitis C.

Conclusions. These findings underscore the importance of medical procedures as risk factors in the current spread of HCV infection in Italy. Because nearly all patients with acute, self-limiting hepatitis C—both symptomatic and asymptomatic—have spontaneous viral clearance within 3 months of disease onset, it seems reasonable to start treatment after this time period ends to avoid costly and useless treatment.

The epidemiology of acute hepatitis C has changed during the past decades, and the incidence of new infection has decreased in most developed countries. The introduction of more accurate and sensitive screening tests has led to the control of hepatitis C associated with blood transfusion and administration of blood derivatives [1]. Moreover, the general improvement in hygiene and sanitary conditions and the campaign for prevention of HIV infection have all contributed to the decrease in the incidence of new infections.

Nevertheless, new cases of hepatitis C still occur each year. In the United States, 40,000 cases of acute hepatitis C virus (HCV) infection per year are currently reported [2]. In Italy, according to data from the national surveillance system specifically for acute viral hepatitis (Sistema Epidemiologico Integrato dell'Epatite Virale Acuta), the incidence of acute HCV infection has decreased from nearly 3 cases per 100,000 population in 1989 to 1 case per 100,000 in 2001 [3]. However, this figure is probably underestimated, because it mainly

Received 24 April 2006; accepted 16 June 2006; electronically published 27 September 2006.

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Clinical Infectious Diseases 2006; 43:1154–9

1058-4838/2006/4309-0005$15.00

Table 1. Demographic, clinical and serological characteristics of 214 patients with acute hepatitis C.

Characteristic	Patients
Age	
Mean years ± SD (range)	37.5 (17–83)
⩽30 years old	100 (46.7)
31–45 years old	52 (24.3)
>45 years old	62 (29.0)
Sex, no. male/no. female	140/74
Region of residence	
Northern Italy	83 (38.8)
Central Italy	40 (18.7)
Southern Italy or the islands	91 (42.5)
Symptoms	
Any	146 (68)
Jaundice	121 (57)
Bilirubin level, mean mg/dL ± SD (range)	4.63 ± 5.6 (0.42–36.76)
Baseline ALT level,[a] mean IU/mL ± SD (range)	1302.8 ± 865.2 (100–4400)
HCV genotype	
1a	24 (11.2)
1b	66 (30.8)
2a/2c	42 (19.6)
3	35 (16.4)
4	4 (1.9)
NA	43 (20.1)
Anti-HCV seroconversion	135 (63.1)
Presence of HBsAg	
Detected	2 (0.9)
Not detected	210 (98.2)
NA	2 (0.9)
HIV status	
Infected	6 (2.8)
Uninfected	164 (76.6)
Undetermined	44 (20.6)
Presence of anti-HBc	
Detected	33 (15.4)
Not detected	164 (76.6)
Undetermined	17 (8.0)
Follow-up, mean months ± SD (range)	14 ± 15.8 (6–74)

NOTE. Data are no. (%) of patients, unless otherwise indicated. ALT, alanine aminotransferase; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NA, not available.

[a] Normal value, ⩽40 IU/mL.

refers to symptomatic patients; it is well known that the majority of acute HCV cases are asymptomatic and, therefore, elude clinical observation. In agreement with this hypothesis, a higher incidence of 2.4 cases per 100,000 population was found in a study conducted with periodic blood donors [4]; moreover, a figure as high as 14 cases per 100,000 population has been reported in a random sample of the general population [5]. Taking into account these considerations, it is accurate to say that several thousand new cases occur each year in Italy.

These findings underscore the importance of determining the current patterns of HCV transmission to obtain a complete and updated picture of the potential sources of infection. Moreover, because acute hepatitis C progresses to chronic infection in 43%–86% of patients [6] and because there is clear evidence that antiviral therapy during the acute phase of HCV infection significantly reduces evolution to chronic illness [7, 8], the identification of patients with newly acquired hepatitis C is useful to the prevention of chronic hepatitis.

Table 2. Potential non–mutually exclusive risk factors for hepatitis C virus transmission.

Risk factor	No. (%) of patients
Intravenous drug use	84 (39.3)
Medical procedure	
Any	144 (67.3)
Hospitalization	67 (31.3)
Surgery	33 (15.4)
Blood transfusion	7 (3.3)
Endoscopy	16 (7.5)
Dialysis	3 (1.4)
Dental treatment	13 (6.1)
Other invasive procedures	5 (2.3)
Needlestick injury	14 (6.5)
Tattoo and/or body piercing	8 (3.8)
Sexual contact	67 (31.3)
Household contact	9 (6.1)
Unknown	28 (13.1)

The aims of this study were first, to evaluate the current sources of HCV transmission in a large Italian cohort of acute hepatitis C patients; second, to assess the factors associated with chronicity and the rate of chronic infection; and finally, to determine the time lag between disease onset and spontaneous resolution.

PATIENTS AND METHODS

Patients. A total of 214 patients with acute hepatitis C treated from 1999 to 2004 in 12 Italian health care centers throughout the country were enrolled in the study. Each patient provided written, informed consent before entering the study. Diagnosis of acute hepatitis C was based on the presence of HCV RNA in serum samples, plus either HCV antibody seroconversion within a 6-month period or alanine aminotransferase levels that were >20 times the upper limit of normal in previously healthy subjects, without any other cause of acute liver damage. These strict criteria were adopted to exclude patients with exacerbation of chronic hepatitis C. Onset of acute hepatitis was established at the time of the first detection of increased serum alanine aminotransferase levels.

We collected information regarding demographic and clinical characteristics and potential risk factors for each patient. The potential risk factors considered were intravenous drug use, history of medical procedures (e.g., hospitalization, surgery, endoscopy, dialysis, blood transfusion, dental treatment, or other invasive procedures), needlestick injury, sexual contact, tattoos and/or body piercing, and household contact. When no risk factor was recorded within the 6 months prior to onset of acute hepatitis C, the source of infection was considered to be unknown.

All patients were followed up, and periodic biochemical and virological tests were performed weekly during the first month after onset of hepatitis, once a month for an additional 5 months, and once every 3 months thereafter. Patients with spontaneous virological and biochemical resolution within 6 months of onset that lasted for at least another 6 months of follow-up (range, 6–74 months) were considered to have self-limiting hepatitis, whereas patients who remained viremic 6 months after onset of infection with persistently high or fluctuating alanine aminotransferase levels were considered to have chronic hepatitis, and they were offered antiviral treatment. In Italy, IFN treatment of acute hepatitis C has been funded by the national health service since 2005.

Virological assays. Serological markers for hepatitis A virus, HCV, hepatitis B virus, and HIV infections were tested for with commercially available kits (Sorin Biomedica and Ortho Diagnostic Systems). Quantitative detection of HCV RNA was performed using a PCR assay with a sensitivity limit of 600 IU/mL (Amplicor HCV-Monitor; Roche Diagnostic Systems) or using a branched-DNA assay with a sensitivity limit of 615 IU/mL (HCV RNA 3.0 Assay; Bayer). Samples that had a sensitivity below the limit that could be detected by quantitative assays were tested using a qualitative PCR assay with a sensitivity limit of 50 IU/mL (Amplicor HCV; Roche Diagnostic Systems). HCV genotyping was performed using a line probe reverse hybridization assay (INNO-LIPA HCV; Innogenetics).

Statistical analysis. Crude ORs for the association of the likelihood of chronicity with the risk factors considered were evaluated by univariate analysis. To identify independent pre-

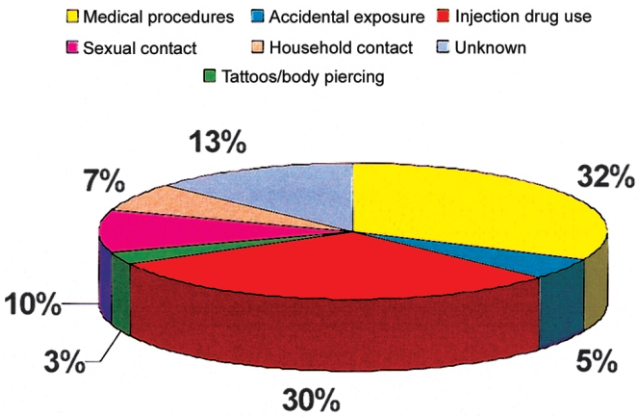

Figure 1. Risk factors for acquiring hepatitis C virus infection (when >1 risk factor was reported, a hierarchy was employed, and only the risk factor associated with the most efficient mode of HCV transmission was recorded).

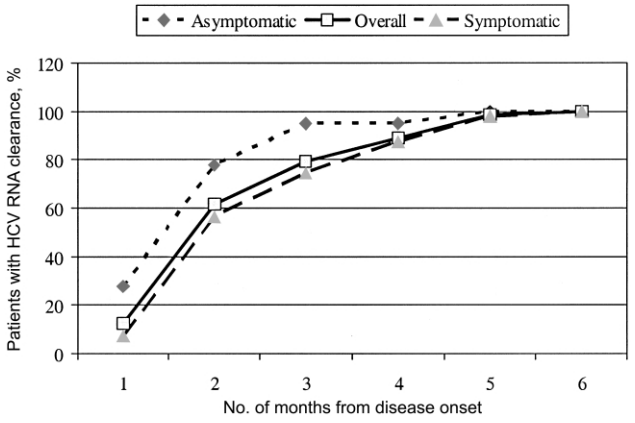

Figure 2. Cumulative frequency over time of 73 patients with spontaneous resolution of acute hepatitis C.

dictors of the likelihood of chronicity, adjusted ORs were calculated by multiple logistic regression analysis.

RESULTS

During 1999–2004, a total of 214 consecutive patients with acute hepatitis C were recruited into the study. Table 1 shows demographic, clinical, and serological features of the study population. In all, 83 patients (38.8%) resided in northern Italy, 40 (18.7%) resided in central Italy, and 91 (42.5%) lived in the south or on the islands. The mean age was 37.5 years, and the majority of patients (65.4%) were male. Symptomatic disease was observed in 148 (68%) of 214 patients; 121 (57%) had jaundice, and 27 (12%) had a bilirubin level >10 mg/dL (1 patient had a maximum level of 36.76 mg/dL). Alanine aminotransferase levels were >20 times the upper limit of normal in 156 patients (73%) and were >50 times the upper limit of normal in 39 (18%; the peak level of 1 patient was 110 times the upper limit of normal). The most common genotype detected was 1b (detected in 66 patients [30.8%]). The diagnosis of hepatitis C was made on the basis of seroconversion in 135 (63.1%) of 214 patients. In patients in whom no anti-HCV antibodies were detected 6 months before the onset of acute hepatitis C, testing for anti-HCV antibodies was performed because of the presence of risk factors (such as drug addiction or accidental exposure) or as part of laboratory procedures for the diagnosis of other diseases. Two patients had detectable hepatitis B surface antigen, and 6 had HIV infection. No patient experienced fulminant disease.

Potential non–mutually exclusive risk factors experienced during the 6 months before onset of acute HCV infection were reported by 186 patients (87%). The most frequent risk factors were intravenous drug use, medical procedures, and sexual contact (including >2 partners in the previous 6 months), sexual promiscuity, sex with a person with HCV infection, and men who have sex with men (table 2). Medical procedures that were risk factors included hospitalization, surgical intervention, endoscopy, blood transfusion, dialysis, dental treatment, and other invasive diagnostic or therapeutic procedures. Among patients who underwent surgery, abdominal, cardiovascular, orthopedic, and ophthalmological interventions were the most commonly reported (data not shown). Sixteen patients underwent endoscopy (9 gastroscopies, 4 colonoscopies, 3 bronchoscopies, and 1 arthroscopy); biopsies were performed for 10 patients. When >1 risk factor was reported, a hierarchy was employed, and only the risk factor associated with the most efficient mode of HCV transmission was recorded. Overall, among 214 patients with acute hepatitis C, 69 (32%) reported undergoing at least 1 medical procedure, and 64 (30%) were intravenous drug users (figure 1).

Stratifying patients according to geographic area of residence, we noted that medical procedures performed in southern Italy and intravenous drug use by patients in the central and northern regions were the most frequent risk factors observed (data not shown). No risk factor was reported or identified in 13% of patients.

In 203 patients who were available for the 6-month follow-up, the outcome of acute hepatitis C was evaluated. A total of 73 patients (36%) showed spontaneous resolution of illness, and 130 (64%) became chronic HCV carriers. The percentage of subjects with self-limiting acute hepatitis C was 41% for symptomatic patients but 26% for asymptomatic patients ($P < .04$). The average time from disease onset to spontaneous resolution was 71 days (range, 27–173 days). Interestingly, 80% of the 73 patients with self-limiting hepatitis had HCV RNA clearance within 3 months of disease onset, and 90% had clearance within 4 months (figure 2). HCV RNA clearance occurred earlier in the 18 patients with asymptomatic self-limiting acute hepatitis than it did in the 55 patients with symptomatic self-limiting infection (figure 2). The outcomes of acute hepatitis C according to genotype are shown in table 3. Patients with genotype 3 infection experienced the highest rate of spontaneous resolution. After exclusion of patients without documented anti-HCV seroconversion, the percentage of subjects

Table 3. Outcome of acute hepatitis C, by genotype.

		No. (%) of patients	
Genotype	No. of patients	Resolution of hepatitis C	Progression to chronic hepatitis C
1a	22	8 (36)	14 (74)
1b	63	21 (33)	42 (77)
2a/2c	42	11 (26)	31 (74)
3	32	13 (41)	19 (59)
4	4	0 (0)	4 (100)

Table 4. Frequency of risk factors reported by patients with acute hepatitis C, by illness outcome.

Factor	Self-limited illness, % (n = 73)	Progression to chronic illness, % (n = 130)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex				
Female	38.3	31.5	1	1
Male	61.7	68.5	1.3 (0.7–2.5)	1.5 (0.7–3.1)
Age				
⩽30 years	45.2	46.1	1	1
>30 years	54.8	53.9	1.0 (0.5–1.7)	0.9 (0.4–2.0)
Asymptomatic disease	24.6	39.2	2.0 (1.0–3.8)	1.8 (0.8–3.8)
HCV genotype				
Non-1	67.2	65.6	1	1
1	32.8	34.4	1.1 (0.6–2.0)	1.1 (0.5–2.2)
Anti-HBc detection	10.6	21.0	2.2 (0.9–5.6)	2.5 (0.8–7.4)
Route of transmission				
Intravenous drug use	42.9	31.0	0.6 (0.3–1.2)	0.5 (0.2–1.0)
Other	57.1	69.0	1	1

NOTE. Crude and adjusted ORs were adjusted by multivariate analysis for all the variables listed in the table, for the association of the likelihood of progression to chronic disease with potential risk factors. HBc, hepatitis B core antigen; HCV, hepatitis C virus.

who experienced resolution of infection did not change. The 2 patients in whom hepatitis B surface antigen was detected experienced resolution of acute hepatitis C and remained hepatitis B virus chronic carriers. Moreover, 3 of the 6 HIV-infected patients with HCV superinfection experienced resolution of HCV disease. Multiple logistic regression showed that none of the variables considered (including asymptomatic disease) were associated with the likelihood of chronicity (table 4).

DISCUSSION

In this study, a large cohort of 214 patients with acute hepatitis C was recruited over 5 years (1999–2004) to evaluate the current modes of HCV transmission and the outcome of sporadic or community-acquired acute hepatitis C. Because data were obtained from several hospitals in different parts of the country using homogeneous diagnostic procedures, the epidemiological picture provided herein can be considered to be representative of the population of Italy.

The present study shows that intravenous drug use and invasive medical procedures are the main modes of HCV transmission in Italy. These findings are in agreement with the corresponding figures from Sistema Epidemiologico Integrato dell'Epatite Virale Acuta, which identified intravenous drug use (OR, 35.5; 95% CI, 23.1–54.4) and surgical intervention (OR, 4.6; 95% CI, 3.3–6.5) as the strongest independent predictors of acute hepatitis C in Italy during 1994–1996 [9]. The importance of medical procedures in the spread of HCV in the absence of an effective vaccine emphasizes the need for the implementation of generic preventive measures aimed at controlling this source of exposure. Naturally, this is possible only if people are aware of the importance of medical procedures as a mode of transmission and then enact a more-precise surveillance program to identify the exact medical practices leading to infection. Medical procedures have also been reported to play a role in HCV transmission in other studies, with a reported range of incidence of transmission of 16%–69% [7, 10–12].

In our study, the rate of acute hepatitis C that became chronic hepatitis C was 64%, a figure not far from the 67% [13] or the 71% [14] observed in 2 previous Italian studies of smaller cohorts. Some studies have identified symptomatic disease as a predictor of spontaneous viral clearance, presumably reflecting a more effective host immune response that is capable of eradicating the virus by killing infected hepatocytes and is responsible for clinical manifestations [15]. However, in 1 study that revealed in univariate analysis that jaundice was a prognostic factor of self-limiting hepatitis ($P < .04$), the authors failed to adjust for the influence of confounders by multiple logistic regression analysis [13]. In another study, in which all asymptomatic patients developed chronic hepatitis C, results may have been biased by the small sample size (only 9 asymptomatic patients were enrolled) [10]. Even in the present study, which includes a large cohort of patients with acute HCV infection, spontaneous HCV RNA clearance was more likely to be observed in symptomatic patients than in asymptomatic patients in univariate analysis ($P < .04$). However, after adjustment for the disturbing influence of confounders by multiple logistic

regression analysis, asymptomatic disease was no longer associated with the likelihood of chronicity (OR, 1.8; 95% CI, 0.8–3.8). Similar results were obtained in a recent prospective study of 34 consecutive patients with acute HCV infection in Italy [14].

It has been suggested that host-related factors—in particular, cell-mediated immunity—play a crucial role in the spontaneous clearance of the virus. There is clear evidence that early, vigorous, sustained $CD4^+$ cell Th1 responses are associated with viral clearance [16]. Moreover, broad cell-mediated immunity within the first month after onset of symptoms represents an efficient predictor of viral clearance [14]. The observation that HCV RNA clearance was more likely to occur earlier among subsets of patients with asymptomatic disease, rather than among those with symptomatic acute hepatitis C, may reflect a length-time bias; the true time of disease onset in patients with asymptomatic cases might have been earlier than that recorded, and in symptomatic patients, it may correspond almost exactly to what was recorded.

One of the main issues is the definition of the optimal time to start treatment of acute hepatitis C. Is it better to initiate immediate treatment, or is it better to delay treatment in order to treat only those patients in whom HCV RNA remains detectable after 12 weeks from disease onset, a period of time after which a spontaneous clearance is unlikely to be achieved? Progression to chronic illness should be prevented, but costly and useless treatment of patients whose illness would spontaneously resolve should be avoided. Thus, the risks and benefits of antiviral treatment should be carefully balanced. It has been shown that delaying therapy until 8–12 weeks after the onset of disease does not compromise the response to IFN treatment, because starting therapy later yields the same rate of response as earlier treatment [17]. However, it has been suggested that, in contrast with patients who have symptomatic, acute HCV infection, those with asymptomatic disease should receive immediate antiviral treatment, because they have little chance of achieving spontaneous viral clearance [10]. Our results show that nearly all persons with acute, self-limiting hepatitis C, either symptomatic or asymptomatic, experience spontaneous HCV RNA clearance within 3 months after disease onset. On the basis of these findings, it seems reasonable to suggest that antiviral treatment be started 3 months after disease onset, regardless of the presence of symptoms.

In conclusion, knowledge of the current sources of HCV transmission may help to define more effective prevention strategies and surveillance programs for high risk populations. This would enable early detection of illness and eventual treatment of newly acquired hepatitis C.

Acknowledgments

We acknowledge the other authors of this article: M. Fasano, A. Guastadisegni, and S. Palattella (Clinic of Infectious Diseases, University of Bari, Bari, Italy); M. P. Riccardi (Malattie Infettive, Grosseto, Italy); O. Bargiacchi (Department of Infectious Diseases, University of Turin, Turin, Itlay); A. Carlotto (Department of Infectious Diseases and Tropical Medicine, S. Bortolo Hospital, Vincenza, Italy); and M. Mazzola (Division of Infectious Diseases, Bisceglie Hospital, Bisceglie, Italy). We also are grateful to Ms. Paulene Butts for her assistance in the preparation of the manuscript.

Potential conflicts of interest. All authors: no conflicts.

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