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研究報告の概要

2000年8月から2002年10月に三次ケアセンターの肝疾患病棟におけるC型肝炎ウイルス（HCV）の院内感染をプロスペクティブに調査した。入院患者のHCV感染有病率の中央値は50%であった。退院後6ヶ月目にHCV感染の血清マーカーを測定し、すでに判明しているHCV感染の危険因子について記録した。1504名中1301名（84.5%）から完全な追跡データが得られ、6名（0.46%）がHCVに感染していた。HCV遺伝子解析によると、HCV感染患者と同じ病室の患者（3例）、同一の看護チームによるケアを受けている患者（1例）が感染源として特定された。HCV獲得に最も関与する危険因子は、入院期間（>10日間、OR 35、95%CI 1.96〜622）とHCV感染患者と同じ病室になること（>5日間、OR 12、95%CI 1.39〜103）であった。実際に、HCV感染は11日以上入院している患者357名のうち1.7%で発生した。結論として、HCVの院内感染は肝疾患病棟、特に長期間の入院を要する患者において、患者から患者のルートで発生しているようである。予防措置の強化とリスクの高い患者を隔離することがHCVの院内感染を更に減少させることにつながるかもしれない。

報告企業の意見	今後の対応
HCVの感染は肝疾患病棟、特に長期間の入院を要する患者において、患者から患者のルートで発生しているようであるとの報告であることから、輸血後 HCV 感染症の調査には、院内感染など輸血以外の伝播ルートについて考慮する必要がある。	日本赤十字社は平成16年8月28日よりNATの感度を上昇させるためプールサイズを50から20へ変更した。HCV感染の新たな伝播ルート等について、今後とも情報の収集に努める。

使用上の注意記載状況・その他参考事項等

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血液を介するウイルス、細菌、原虫等の感染
vCJD 等の伝播のリスク

Nosocomial Transmission of HCV in the Liver Unit of a Tertiary Care Center

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Despite its medical and legal implications, there are no prospective studies analyzing the incidence and mechanisms involved in the nosocomial transmission of hepatitis C virus (HCV) in liver units. This study prospectively investigates the nosocomial transmission of HCV in the liver unit of a tertiary care center from August 2000 to October 2002. The median prevalence of HCV infection among hospitalized patients was 50%. Anti-HCV–negative patients admitted to the liver unit during the study period were prospectively followed, and serum markers of HCV infection were repeated 6 months after discharge. All known risk factors for HCV transmission (including the physical allocation of HCV-infected and noninfected patients during hospitalization) were recorded. Complete follow-up data were available in 1,301 (84.5%) of 1,540 patients. Six patients (0.46%) acquired HCV infection (annual incidence: 0.27/100 admissions). Phylogenetic analyses of recovered HCV sequences identified the source of infection as an HCV-infected roommate (3 cases) and a patient receiving care by the same nurse team (1 case). The most relevant risk factors associated with HCV acquisition were duration of hospitalization (>10 days; OR, 35; 95% CI, 1.96-622) and hospitalization with an HCV-infected roommate (>5 days; OR, 12; 95% CI, 1.39-103). In fact, HCV infection occurred in 1.7% of the 357 patients hospitalized longer than 10 days. In conclusion, HCV nosocomial infection appears to occur via patient-to-patient transmission in liver units, particularly in individuals who require long hospitalizations. Continuous reinforcement of universal prevention measures and, when possible, isolation of patients at higher risk might further reduce nosocomial HCV transmission. (HEPATOLOGY 2005;41:115–122.)

Among the most relevant risk factors for hepatitis C virus (HCV) acquisition are injection drug use, birth to an infected mother, multiple heterosexual partners and transfusion of blood or blood products before 1990.[1,2] Transmission of HCV has been reported in individual cases related to diagnostic and therapeutic procedures, as well as in circumscribed epidemics resulting from unsafe injection practices or contaminated equipment.[3–6] Transmission of HCV by an infected health care worker is a very rare event and has been essentially linked to surgery or medical care.[7,8] Although health care–related procedures have not been unequivocally associated with HCV acquisition in case–control studies,[2] some studies have demonstrated a higher prevalence of HCV infection in patients who underwent invasive medical procedures or prolonged hospitalization.[9,10]

Transmission of HCV in hemodialysis and hematology units is well documented.[6,11,12] Transfusion of blood products before universal anti-HCV screening and patient-to-patient transmission have been implicated as the main mechanisms of HCV acquisition in this setting.[12–15] The latter mechanism was suspected by the greater incidence of HCV transmission in units with higher prevalence of HCV infection and has been unequivocally demonstrated by molecular analysis of HCV isolates.[16] Implementation of universal precaution measures and isolation of HCV-infected from noninfected patients re-

Abbreviation: HCV, hepatitis C virus.

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sulted in a significant decrease of HCV transmission in hemodialysis units.[17-19]

Because of the high prevalence of HCV infection among patients with cirrhosis, hepatology wards represent a potential high-risk setting for HCV nosocomial spread. Hospitalized HCV-infected patients are not separated from noninfected patients, and medical and nursing staff usually care for both HCV-infected and noninfected patients simultaneously.

We prospectively studied the incidence and mechanisms involved in the nosocomial transmission of HCV in the liver unit of a tertiary care center for a period of more than 2 years. All potential risk factors associated with HCV infection were analyzed, and a thorough epidemiological and molecular analysis of the infected cases was performed.

Patients and Methods

Patients. All patients admitted to the three hospitalization wards of our Liver Unit (Hepatology, Liver Surgery and Transplantation, and Daycare Unit) from August 2000 to October 2002 were screened for anti-HCV. Anti-HCV–negative patients were included in the study. The study was approved by the Local Ethics Committee; all patients received a written synopsis of the aims and methodology of the study and gave their consent for participation.

The Hepatology ward cares essentially for patients with decompensated cirrhosis, whereas the Liver Surgery and Transplantation ward cares for liver transplant recipients and patients with primary or metastasic liver cancer. The Daycare Unit is shared by the Liver and the Gastroenterology units, and patients with liver or gastrointestinal diseases are admitted on a 1-day basis to undergo diagnostic or therapeutic procedures. Medical and nursing staff working at the three hospitalization wards were aware of the aims and methodology of the study. In addition, the Epidemiology Unit of our institution performs regular surveys to ensure full observance of universal precaution measures. Among the common precaution measures used in the units are the routine labeling of HCV infection in the nursing flow sheets, hand washing and change of gloves before and after each patient manipulation, disinfections of nondisposable material (*e.g.*, tourniquets) if used for venous blood sampling, and the nonuse of multidose vials. Capillary blood glucose levels were monitored using an Accu-Chek device (Roche Diagnostics, Barcelona, Spain); patients' fingers were never placed directly on the blood glucose meter. Patients requiring special attention—such as those with major gastrointestinal bleeding or sepsis—are moved into individual rooms and, when necessary, an extra fully dedicated nurse takes care of the patient until the patient is transferred to the intensive care unit or is stabilized.

For anti-HCV–negative patients and during the time of admission, all known risk factors associated with nosocomial transmission of hepatitis C were carefully recorded, including: (1) transfusion of blood products; (2) invasive procedures such as diagnostic endoscopy (gastroscopy, colonoscopy, and endoscopic retrograde cholangiopancreratography), therapeutic endoscopy (variceal sclerosis and banding, polypectomy), angiography and transcutaneous arterial embolization, other radiological procedures requiring intravenous contrast, liver biopsy, percutaneous ethanol injection, radiofrequency ablation, transhepatic cholangiography, hepatic hemodynamics studies and transcutaneous intrahepatic portosystemic shunt, and large volume paracentesis; and (3) minor and major surgical interventions.

Duration of hospitalization was registered for each patient; in individuals admitted more than one instance, the total number of days of hospitalization was considered for analysis. Patient allocation in the different wards was registered every day to identify anti-HCV–positive roommates and the nurse team who was in charge of each patient. A nurse team was defined as all nurses from different shifts (morning, afternoon, night, and weekends) in charge of the same beds (and therefore caring for the same patients). This figure includes registered nurses, licensed practical nurses, and aides.

Anti-HCV was reexamined 6 months after patients' discharge. In patients with more than one hospital admission, anti-HCV was examined at each admission and 6 months after each discharge. If the patient lived outside the Barcelona area, we addressed a letter to the primary care physician asking for a follow-up anti-HCV test. In patients who seroconverted to anti-HCV, infection was confirmed by determination of HCV RNA by a sensitive qualitative assay (Amplicor HCV 2.0; Roche Diagnostics, Branchburg, NJ). In immunocompromised patients, such as patients who underwent liver transplantation or who were under chemotherapy, serum aminotransferases were determined at 3, 6, and 12 months after hospital discharge, and, if elevated, HCV RNA was determined even in the absence of anti-HCV seroconversion.

In case of confirmed HCV infection, a complete epidemiological study based on our records was carried out. Patients were carefully interviewed for lifestyle practices and anti-HCV status of family members. If the patient received blood products, the blood bank was contacted to identify all implicated donors. HCV infection was ex-

cluded by serological follow-up of donors and/or by repeating anti-HCV and HCV RNA in stored plasma samples. All anti-HCV–positive (or HCV RNA–positive) individuals who shared a room or nurse with patients who acquired HCV during the study were identified, and a serum sample was obtained when necessary. In patients submitted to invasive procedures, we identified those individuals who had undergone the same procedure on the same day and were anti-HCV–positive; a serum sample was obtained and, if necessary, analyzed. If the source of HCV infection could not be identified, the anti-HCV status of health care staff involved in patients' care was investigated.

HCV sequences from patients who acquired the infection during the study and from individuals with the highest probability to be the source of infection (anti-HCV–positive roommates or individuals who shared the same nurse team) were included in a phylogenetic analysis. If this analysis failed to identify the source of infection, molecular analysis was expanded to other likely sources, such as anti-HCV–positive patients who were simultaneously admitted to the same ward or individuals who underwent the same invasive procedure at the same session.

HCV RNA, Genotype, and Serotype Determination. HCV RNA was determined with a sensitive qualitative assay (Amplicor HCV 2.0). HCV genotype was determined by restriction fragment length polymorphism after amplification of the 5′ noncoding region of the HCV genome, as described previously.[20]

If HCV RNA was undetectable, HCV genotype was determined with a serotyping assay that detects type-specific antibodies directed to epitopes encoded by the NS4 region of the genome (Murex HCV Serotyping; Abbot Cientifica S.A., Madrid, Spain). The assay identifies the HCV type (1-6) with high accuracy but does not provide information on the HCV subtype.[21]

Phylogenetic Analysis. A phylogenetic analysis of HCV sequences was performed to determine if different patients were infected with closely related strains. Partial amplification of the E1 and E2 regions (392 nucleotides encompassing a fragment of the E1 and E2, including the hypervariable region 1) was performed as described elsewhere.[5] Amplified fragments were purified, and bidirectional sequence analysis was performed using a commercial kit (Perkin-Elmer Applied Biosystem, Warrington, United Kingdom). Sequence alignment and phylogenetic analysis were performed using the Neighbor Joining program in the PHYLIP package as described previously (Bootstrap support 1000 random resamplings of the sequences K2p (Ti/Tv=2), unrooted).[5]

Table 1. Baseline Characteristics of Patients Included in the Study According to Their Status at the End of Follow-Up

	Completed Follow-Up (n = 1,301)	Died (n = 123)	Lost to Follow-Up (n = 116)
Age*	57 (16-94)	64 (30-92)	59 (19-90)
Male sex (%)	811 (62%)	79 (64%)	72 (62%)
Days of admission†	2 (1-121)	9 (1-82)	1 (1-37)
Baseline disease‡			
Chronic hepatitis	138 (11%)	0	12 (10%)
Cirrhosis	292 (22%)	46 (37%)	16 (14%)
Hepatocellular carcinoma§	101 (8%)	32 (26%)	6 (5%)
Liver transplantation‖	111 (8%)	2 (2%)	5 (4%)
Benign gastrointestinal disease	385 (30%)	6 (5%)	38 (33%)
Digestive cancer	117 (9%)	23 (19%)	9 (8%)
Benign biliary disease	125 (10%)	11 (9%)	28 (24%)
Other	32 (2%)	3 (2%)	2 (2%)

NOTE. Quantitative variables are expressed as median (range).

*Patients who died were significantly older than patients who completed follow-up ($P < .01$).

†Patients who died were admitted for a longer period than patients who completed follow-up ($P < .01$).

‡Differences in baseline diseases among the three groups were statistically significant ($P < .01$).

§Includes patients with cholangiocarcinoma.

‖Includes patients who underwent transplantation before study initiation and required hospitalization.

Statistical Analysis. We analyzed the data with SPSS version 10 software (SPSS Inc., Chicago, IL). Quantitative variables are expressed as the median (range). For quantitative variables, differences between groups were analyzed using a nonparametric test (Mann-Whitney). For categorical variables, differences between groups were calculated using the Fisher exact test. To identify risk factors of nosocomial HCV acquisition, odds ratios and their respective 95% CIs were calculated (OR ± 1.96 SE).

Results

Follow-Up. During the study period, 1,540 anti-HCV–negative patients were admitted to the different wards, corresponding to a total of 2,436 hospital admissions. Follow-up anti-HCV serology was available in 1,301 (84.5%) of the 1,540 patients and in 2,186 (89.7%) of the total number of admissions. One hundred twenty-three patients (8%) died within the scheduled 6-month follow-up, and 116 patients (7.5%) did not return for the follow-up anti-HCV test. Baseline features of the three groups are summarized in Table 1. As expected, patients who died prematurely had a significantly higher prevalence of cirrhosis and malignant diseases and longer admission periods compared with patients belonging to

Table 2. Baseline Characteristics and Follow-Up Data on the 6 Patients Who Acquired HCV Infection During the Study Period

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (yrs)	48	68	55	46	27	46
Sex (M/F)	M	M	M	F	M	F
Baseline disease	LT (alcoholic cirrhosis)	Disseminated rectal adenocarcinoma	LT (alcoholic cirrhosis)	Disseminated colonic adenocarcinoma	Living donor (right hepatic lobe)	Decompensated alcoholic cirrhosis
Anti-HCV seroconversion	Yes (after 1 yr)	Yes	No	Yes	Yes	Yes
HCV viral load at time of detection (IU/mL)	180,000	46,200	2,030,000	883,000	Undetectable	1,410,000
Genotype	1a	3	1b	1b	1*	1b
Peak alanine aminotransferase (IU/L)	775	136	83	752	27	883
Transfusion of blood products	Yes	Yes	Yes	Yes	No	Yes
Surgery	Yes	Yes (×3)	Yes	Yes	Yes	No
Invasive procedures	THC (2), LB	DE, TAE, THC, R (3)	A, THC (2), R	DE, RF, R (6)	A, IU	DE, TE, A, HE (3), LB (2), R
Duration of hospitalization (days)	23	63	44	14	16	60
Anti-HCV–positive roommate (days)	Yes (12)	Yes (44)	Yes (23)	No	Yes (9)	Yes (20)
Outcome of HCV infection	Cirrhosis† (retransplantation)	Persistent infection	Chronic hepatitis†	Persistent infection	Spontaneous resolution	Resolution after therapy

Abbreviations: M, male; F, female; LT, liver transplantation; THC, transhepatic colangiography; LB, liver biopsy; TAE, transcutaneous arterial embolization; R, radiological procedures; A, angiography; DE, diagnostic endoscopy; RF, radiofrequency ablation; IU, invasive ultrasonography; TE, therapeutic endoscopy; HE, hepatic hemodynamics.

*Determined with serotyping assay.

†Diagnosed by liver biopsy.

the other groups. Patients lost to follow-up had a significantly higher prevalence of benign gastrointestinal and biliary diseases when compared with other groups. These patients were mostly referred from centers outside the Barcelona area to undergo interventional endoscopy (endoscopic retrograde cholangiopancreratography and colonic polypectomy); this may explain the relatively low compliance to undergo follow-up anti-HCV serology.

Risk Factors for HCV Acquisition. The prevalence of anti-HCV–positive patients admitted to the three different wards varied daily, but its median value was 50% (45% and 41% in the Hepatology ward and Daycare Unit, respectively, vs. 55% in the Liver Surgery and Transplantation ward; $P < .01$). The median number of days of hospitalization was 1 for the Daycare Unit and 12 for both the Hepatology and Liver Surgery and Transplantation wards. In none of the three hospitalization wards were anti-HCV–positive patients routinely isolated in individual rooms, and nurses cared for anti-HCV–positive and anti-HCV–negative patients simultaneously. The mean number of hours of nursing care per patient day was 6.5.

A total of 1,301 anti-HCV–negative patients with complete follow-up were included in the study. The number of invasive procedures registered during the study period was 4,467. Most of these procedures were diagnostic or therapeutic endoscopies (1,648 including endoscopic retrograde cholangiopancreratography), radiological procedures requiring intravenous contrast (1,175 including angiography), interventional ultrasonographies (583), hepatic hemodynamics (468), large-volume paracentesis (267), and percutaneous or transhepatic colangiographies (253). Four hundred thirty-six patients (33%) underwent surgical procedures (62 liver transplantations), and 249 (19%) received blood products.

Six patients (0.46%) acquired HCV infection during the study period (four in the Liver Surgery and Transplantation ward, one in the Hepatology ward, and one in the Daycare Unit). This number represents an annual incidence of 0.27 cases per 100 admissions. Taking into consideration the total number of beds (46) and the median prevalence of anti-HCV–negative patients (50%), this figure would translate into 11.8 cases of nosocomial HCV infection per 100 treatment years. The baseline characteristics and the potential risk factors of these patients, as well as the most relevant features of HCV infection, are summarized in Table 2. HCV infection was detected via anti-HCV seroconversion in 4 patients, whereas in 2 liver transplant recipients HCV infection was identified via alanine aminotransferase elevation after hospital discharge (anti-HCV became positive after 12 months in one of them). HCV RNA was positive in all but one of the infected individuals at the time of anti-HCV detection or alanine aminotransferase elevation. In the only individual with negative HCV RNA, aminotransferases were within

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Table 3. Risk Factors for HCV Acquisition Identified During the Study Period

	Infected (n = 6)	Noninfected (n = 1295)	*P* Value	Odds Ratio	95% CI
Days hospitalized	33 (14-63)	2 (1-121)	<.001		
Hospitalization >10 d	6 (100%)	351 (27%)	<.001	35	1.96-622
Anti-HCV + roommate	5 (83%)	961 (74%)	.5		
Days hospitalized with anti-HCV + roommate	16 (0-44)	1 (0-49)	.015		
Hospitalization with anti-HCV + roommate >5 d	5 (83%)	389 (30%)	.011	12	1.39-103

NOTE. For zero count cells a 0.5 value was used to calculate odds ratio (95% CI).
Abbreviation: NS, not significant.

the normal range and the presence of anti-HCV was confirmed via recombinant immunoblot assay. We assumed that the patient, who was the living donor of a right hepatic lobe, had hepatitis C but was able to clear HCV. Despite the small number of patients who became infected during the study period, we identified several risk factors for HCV acquisition (Table 3). The most relevant differences between patients who did and did not acquire HCV during the study period were a longer hospitalization (33 days vs. 2 days; $P < .001$), longer hospitalization with anti-HCV–positive roommates (16 days vs. 1 day; $P = .015$), surgery (83% vs. 25%; $P = .005$), and transfusion of blood derivates (83% vs. 19%; $P = .001$). In addition, patients who acquired HCV had undergone more invasive procedures compared with patients who did not acquire HCV (5 vs. 2; $P = .018$). Importantly, HCV infection occurred in 1.7% of the 357 patients who required hospitalization longer than 10 days. The latter group of patients had severe underlying conditions more frequently than patients admitted for a shorter period (cirrhosis, 44% vs. 15%; hepatocellular carcinoma or colangiocarcinoma, 14% vs. 7%; liver transplantation, 18% vs. 4%; $P < .001$ in all cases). In patients with cirrhosis who were hospitalized for more than 10 days, admission for sepsis, refractory ascites, or hepatorenal syndrome was more frequent than for gastrointestinal bleeding or hepatic encephalopathy. As expected, patients who were hospitalized for more than 10 days underwent a significantly higher number of invasive procedures (4 vs. 1; $P < .0001$) and spent more days with an HCV-positive roommate (8 vs. 1; $P < .0001$).

Phylogenetic Analysis. HCV sequences from the 5 patients who became infected during the study (and had detectable HCV RNA) and from individuals with the highest probability to be the source of infection were included in a phylogenetic analysis (Fig. 1). Patient 1 was infected with genotype 1a, patient 2 with genotype 3a, and patients 3, 4, and 6 with genotype 1b.

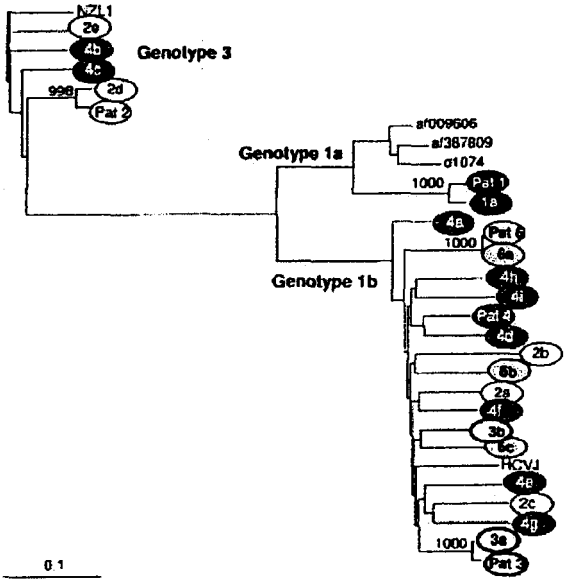

Fig. 1. Phylogenetic tree of partial E2 sequences from patients investigated during the study period. HCV sequences of patients who acquired HCV during the study are depicted in different gray tones (patient 1, patient 2, patient 3, patient 4, and patient 6) and HCV sequences from patients who were investigated as their possible source of infection are represented in the same gray tone, respectively. For patient 1, we included his only roommate (1a); for patient 2, three different roommates (2a, 2b, 2c); for patient 3, two different roommates (3a, 3b); for patient 4 (who did not have HCV-infected roommates), two HCV-infected individuals who shared the same nurse team (4a, 4b); and for patient 6, three different roommates (6a, 6b, 6c). The phylogenetic analysis disclosed that patient 1 and his only roommate (1a), patient 3 and one of his roommates (3a) and patient 6 and one of her roommates (6a) were infected by HCV strains that were genetically very closely related. For patient 2, we expanded the analysis to patients who shared the same nurse team (2d and 2e), and for patient 4, we included HCV sequences from patients who shared a ward during her admission period (4c, 2a, 4d, 4e, 4f, 4g) and from patients who underwent a CT scan and colonoscopy at the same session (4h and 4i). For patient 2, the source of infection was identified as an HCV-infected patient who shared the same nurse team (2d). For patient 4, the source of infection was not identified. Only boostrap values considered significant (higher than 800) are reported; analysis was performed on 1,000 replicates. Because only 2 of the analyzed patients were infected with genotype 1a (patient 1 and 1a), we included three genotype 1a sequences from GeneBank (af009606, af387809, d1074). We also included a prototype 1b HCV-J sequence. A prototype genotype 3 NZL1 sequence is included as the outgroup sequence. Pat, patient.

For patients 1, 3, and 6, the source of infection was identified as their respective HCV-infected roommates. For patient 2, who was infected with genotype 3, phylogenetic analysis disclosed that another genotype 3–infected individual who shared the same nurse team was infected with a genetically very closely related HCV strain. Regretfully, we were not able to find the source of infection for patient 4 despite a thorough molecular analysis (Fig. 1). A careful interview of the patient excluded risk lifestyle practices; her family members were anti-HCV negative. Although the patient had been transfused, follow-up of potentially implicated donors and retesting of their stored samples failed to demonstrate HCV infection in any of them. None of the health care personnel involved in this patient's care was anti-HCV positive. Because this patient had been admitted to other units in the hospital during the study period, we cannot exclude that she acquired HCV in another ward.

Molecular analysis could not be performed in the patient who cleared HCV. Apart from sharing a room with an HCV-infected individual (the recipient of the patient's right hepatic lobe), a thorough interview excluded any other known risk factors for HCV acquisition. Family members living with the patient were anti-HCV negative. In addition, the health care personnel involved in the patient's care during his hospitalization tested negative for anti-HCV. Because of the temporal sequence of events, we presume that this patient became infected during his admission period and that the most likely source of infection was his roommate. This is further supported by the fact that both individuals shared the same HCV genotype, as confirmed with a serotyping assay.

Although it was unfeasible to determine the exact mechanism of patient-to-patient transmission, nurse coordinators in the involved wards performed an exhaustive survey of personnel adherence to universal precaution measures. The following breaches were detected in exceptional occasions: failure to change gloves or wash hands between different patient manipulations, failure to dispose of intravenous catheter tips after manipulation, and failure to sterilize tourniquets. In addition, exchange of personal items (razors, toothbrushes) between patients sharing a room was identified in a few instances.

Discussion

Nosocomial HCV infection has relevant medical and legal implications. Although acute hepatitis C is a potentially curable disease, treatment is expensive, side effects are common, and in some patients, treatment may not be feasible. In patients progressing to persistent infection, treatment is not as effective and the possibility of progression of the disease causes significant concern to the infected individual. As seen in this study, HCV infection can progress rapidly to cirrhosis in immunocompromised patients, such as liver transplant recipients. Except in the rare event in which an HCV-infected health care worker is the source of infection or in cases of circumscribed epidemics,[5,7] demonstration of the mechanism of nosocomial HCV transmission is extremely difficult. Nevertheless, acquisition of HCV infection in the hospital setting can generate long and expensive legal claims.

For various reasons, liver units of tertiary care centers can be considered high-risk settings for nosocomial HCV transmission. First, the prevalence of HCV infection is high in patients admitted to liver units. Second, HCV-infected patients are not physically separated from noninfected individuals; consequently, chances of patient-to-patient transmission do exist. Finally, patients admitted to liver units (*e.g.*, patients with decompensated cirrhosis, recipients of liver transplant) require close nursing care and often undergo invasive diagnostic and therapeutic procedures. Despite the above-mentioned arguments, there are no studies analyzing HCV transmission in liver units.

This prospective study showed that nosocomial transmission of HCV can occur despite careful observation of universal precautionary measures. Although the overall incidence of HCV transmission was low, our results show that certain groups of patients (those with severe underlying conditions requiring long or frequent hospitalizations) are clearly at increased risk of HCV acquisition. Patients who acquired HCV infection underwent surgery, transfusion of blood products and invasive procedures more frequently than patients who did not acquire HCV during the study. However, the latter variables are indicative of severe medical conditions requiring prolonged hospitalizations. In fact, phylogenetic analysis of recovered HCV sequences disclosed that patient-to-patient transmission—not the procedures themselves—was the main mechanism of HCV spread. Importantly, in 3 of the 4 cases in which the source of infection was identified, it corresponded to an HCV-infected roommate.

This study had some limitations. Because the nursing staff was fully aware of the aims and methodology of the study, the implicated personnel was careful in the observance of safe practices. This behavior might have had an impact on the study by underestimating the real incidence of HCV nosocomial infection. Another limitation of the study was that we were not able to precisely identify the mechanisms leading to HCV patient-to-patient transmission. Prolonged hospitalization involves many health-related procedures that increase the risk of patient-to-

patient transmission. The latter might occur via direct transmission through close personal contact of blood or secretions (*e.g.*, during manipulation of intravenous catheters and surgical wounds or during blood sampling) or by accidentally shared contaminated equipment or unchanged gloves. Furthermore, exchange of personal items between patients sharing a room was detected during the study and could explain HCV infection. Clearly, HCV transmission among patients not sharing a room would occur through a vector. Nurses perform most of the procedures involving manipulation of contaminated blood or body fluids; consequently, they appear to be the most likely intermediary of HCV transmission.

Despite the awareness of the health care personnel on the study and the careful observance of safe practices, sporadic breaches of universal precaution measures were detected during the study period. Therefore, continuous reinforcement of adherence to universal precautionary measures is essential to reduce nosocomial HCV transmission.

The total hours of nursing care provided to patients admitted to the different wards can be considered within a normal range.[22] However, licensed practical nurse hours and aide hours are included in this figure. There is a positive relationship between the hours of care given by registered nurses and the length of stay and rates of infections in medical and surgical patients.[22] Therefore, it is likely that increasing the number of hours of care by registered nurses per patient day would have had an impact on HCV patient-to-patient transmission. Another approach aimed at reducing the incidence of HCV spread would be to isolate patients at high risk (those with severe underlying conditions in whom long hospitalization is anticipated) in individual rooms and to prevent nurses from simultaneously caring for HCV-infected and noninfected individuals. The latter would avoid the sharing of potentially contaminated paraphernalia by roommates. We are aware that implementation of the above-mentioned strategies would complicate routine clinical practice and increase the use of resources. However, it is important to stress that the implementation of similar policies in other hospital settings has been successful in reducing the incidence of nosocomial HCV transmission.[17,23]

In summary, the main mechanism of nosocomial HCV transmission in the hospital setting is patient-to-patient transmission. Because its incidence is not high and infection is often asymptomatic, nosocomial HCV infection is usually not identified and probably underestimated. Our data strongly suggest that patients requiring long or frequent hospitalizations are at higher risk of HCV acquisition. Continuous reinforcement of universal prevention rules is essential to prevent nosocomial HCV infection. When possible, isolation of patients at higher risk in individual rooms might be implemented to reduce the risk of HCV acquisition.

The nucleotide sequence data reported herein have been assigned GenBank accession numbers AY769869-769893.

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References

1. Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341:556–562.
2. Alter MJ. Prevention of spread of hepatitis C. HEPATOLOGY 2002; 36(Suppl 1):S93–S98.
3. Bronowicki JP, Venard V, Botte C, Monhoven N, Gastin I, Chone L, et al. Patient-to-patient transmission of hepatitis C virus during colonoscopy. N Engl J Med 1997;337:237–240.
4. Krause G, Trepka MJ, Whisenhunt RS, Katz D, Nainan O, Wiersma ST, et al. Nosocomial transmission of hepatitis C virus associated with the use of multidose saline vials. Infect Control Hosp Epidemiol 2003; 24:122–127.
5. Bruguera M, Saiz JC, Franco S, Gimenez-Barcons M, Sanchez-Tapias JM, Fabregas S, et al. Outbreak of nosocomial hepatitis C virus infection resolved by genetic analysis of HCV RNA. J Clin Microbiol 2002;40:4363–4366.
6. Widell A, Christensson B, Wiebe T, Schalen C, Hansson HB, Allander T, et al. Epidemiologic and molecular investigation of outbreaks of hepatitis C virus infection on a pediatric oncology service. Ann Intern Med 1999; 130:130–134.
7. Esteban JI, Gomez J, Martell M, Cabot B, Quer J, Camps J, et al. Transmission of hepatitis C virus by a cardiac surgeon. N Engl J Med 1996;334: 555–560.
8. Ross RS, Viazov S, Gross T, Hofmann F, Seipp HM, Roggendorf M. Transmission of hepatitis C virus from a patient to an anesthesiology assistant to five patients. N Engl J Med 2000;343:1851–1854.
9. Chiaramonte M, Stroffolini T, Lorenzoni U, Minniti F, Conti S, Floreani A, et al. Risk factors in community-acquired chronic hepatitis C virus infection: a case-control study in Italy. J Hepatol 1996;24:129–134.
10. Mele A, Spada E, Sagliocca L, Ragni P, Tosti ME, Gallo G, et al. Risk of parenterally transmitted hepatitis following exposure to surgery or other invasive procedures: results from the hepatitis surveillance system in Italy. J Hepatol 2001;35:284–289.
11. Allander T, Gruber A, Naghavi M, Beyene A, Soderstrom T, Bjorkholm M, et al. Frequent patient-to-patient transmission of hepatitis C virus in a haematology ward. Lancet 1995; 345:603–607.
12. Forns X, Fernandez-Llama P, Pons M, Costa J, Ampurdanes S, Lopez-Labrador FX, et al. Incidence and risk factors of hepatitis C virus infection in a haemodialysis unit. Nephrol Dial Transplant 1997;12:736–740.
13. Sampietro M, Badalamenti S, Salvadori S, Corbetta N, Graziani G, Como G, et al. High prevalence of a rare hepatitis C virus in patients treated in the same hemodialysis unit: evidence for nosocomial transmission of HCV. Kidney Int 1995;47:911–917.
14. Sanchez-Tapias JM. Nosocomial transmission of hepatitis C virus. J Hepatol 1999;31(Suppl 1):107–112.
15. Struyver L, Claeys H, Wyseur A, Van Arnhem W, De Beenhouwer H, Uytendaele S, et al. Hepatitis C virus in a hemodialysis unit: molecular evidence for nosocomial transmission. Kidney Int 1996;49:889–895.

16. Allander T, Medin C, Jacobson SH, Grillner L, Persson MA. Hepatitis C transmission in a hemodialysis unit: molecular evidence for spread of virus among patients not sharing equipment. J Med Virol 1994;43:415–419.
17. Blumberg A, Zehnder C, Burckhardt JJ. Prevention of hepatitis C infection in haemodialysis units. A prospective study. Nephrol Dial Transplant 1995;10:230–233.
18. Okuda K, Hayashi H, Kobayashi S, Irie Y. Mode of hepatitis C infection not associated with blood transfusion among chronic hemodialysis patients. J Heparol 1995;23:28–31.
19. Jadoul M, Poignet JL. Prevention of hepatitis C virus transmission in hemodialysis. Nephrologie 1997;18:307–308.
20. Lopez-Labrador FX, Ampurdanes S, Forns X, Castells A, Saiz JC, Costa J, et al. Hepatitis C virus (HCV) genotypes in Spanish patients with HCV infection: relationship between HCV genotype 1b, cirrhosis and hepatocellular carcinoma. J Heparol 1997;27:959–965.
21. Pawlotsky JM, Prescott L, Simmonds P, Pellet C, Laurent-Puig P, Labonne C, et al. Serological determination of hepatitis C virus genotype: comparison with a standardized genotyping assay. J Clin Microbiol 1997; 35:1734–1739.
22. Needleman J, Buerhaus P, Mattke S, Stewart M, Zelevinsky K. Nurse-staffing levels and the quality of care in hospitals. N Engl J Med 2002;346: 1715–1722.
23. Fabrizi F, Lunghi G, Guarnori I, Raffaele L, Crepaldi M, Pagano A, et al. Incidence of seroconversion for hepatitis C virus in chronic haemodialysis patients: a prospective study. Nephrol Dial Transplant 1994;9:1611–1615.