Follow-up study of hepatitis C virus infection in uremic patients on maintenance hemodialysis for 30 months

Nian Song Wang¹, Lu Tan Liao², Yan Juan Zhu², Wei Pan³ and Fang Fang³

Subject headings hepatitis C virus; hemodialysis; blood transfusion; cross infection; polymerase chain reaction; risk factors; follow-up studies

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INTRODUCTION

A high prevalence of antibodies to hepatitis C virus (HCV) (range from 3.3% - 80%) has been reported in hemodialysis (HD) patients¹-²⁰, and worrisome as it often becomes chronic and induces chronic liver disease²¹-²⁴, therefore the nephrologists face a major challenge of how to prevent it. The main route of HCV transmission is parenteral, and most cases of HCV infection are thought to be related to blood transfusion, intravenous drug addiction, or HIV infection²²-²⁴, but an increased prevalence of anti-HCV has also been reported in non-transfused HD patients without identifiable risk factors¹,²,⁵,⁶,⁹-¹²,¹⁵,¹⁸,²⁵,²⁶. In fact, some recent reports and our report outline that HCV-negative patients who shared dialysis machines with HCV-positive patients were seroconverted within HD period¹,⁵,¹²-¹⁶,²⁵-²⁶. We undertook a prospective study to assess the incidence and the risk factors for HCV infection in HD patients.

MATERIALS AND METHODS

Subjects

A total of 346 patients at our HD center followed up from June 1, 1995 to December 1, 1997, and 63 patients in June 1995 were included in the study.

¹Department of Nephrology, Shanghai Sixth People’s Hospital, Shanghai 200233, China
²Department of Nephrology, Zhang Shan Hospital, Shanghai Medical University, Shanghai 200032, China
³Department of Microbiology, The Second Military Medical University, Shanghai 200433, China

Nian Song Wang, got a doctorate degree in 1997 in Shanghai Medical University, now associate professor of internal medicine, having 19 papers published.

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Correspondence to: Dr. Nian Song Wang, Department of Nephrology, Shanghai Sixth People’s Hospital, Shanghai 200233, China
Tel 0086-21-64369181 Ext. 8335
Email: Niansong@public8.sta.net.cn

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They were dialyzed for 1 to 92 (mean 23.4) months. Their age ranged from 20-76 years (mean 44.7 years).

From June 1995 to November 1995, December 1995 to May 1996, June 1996 to November 1996, December 1996 to May 1997, June 1997 to November 1997, additional 42, 39, 45, 65 and 71 new patients were included, respectively. Of these 262 patients, 226 had recently started HD, 15 resumed HD after a transplantation failure and 21 had been transferred from other units. Their age range was similar to that of previously included patients. In December 1997, 21 patients who recently started HD, were included, their age range was similar to that of previously included patients.

In June 1996, the sera of 62 patients were tested for anti-CHVIgM, anti-CHVIgG and HCV RNA. Among them, 38 were males and 24 females, their age ranged from 16-71 years (mean 44.6 years), mean duration of HD was 16.1±7.6 months (1-96).

Anti-HCV antibodies

All patients at our HD center were tested every 3 months for the presence of anti-HCV antibodies during the follow-up period. All blood samples were obtained before HD, and were centrifuged, serum stored at -80°C until testing. The kits for examining anti-CHVIgM and anti-CHVIgG were purchased from Shanghai Chang Zhang Chemical Reagent Company, and were tested by the Labor atory of Microbiology, The Second Military Medical University.

HCV RNA

Primers were designed from the conserved 5’-noncoding (5’-NC) region of the HCV genome. S1: 5’-CAGGCCCATGCTATACCTGTC-3’, AS1: GGTGCCTACGAGGCC-3’, S2: 5’-ACTCCCTGCAGAGGCTAC-3’, AS2: 5’-CTCGCAAGCACCCTTATCAGG-3’. A RT-PCR assay procedure was performed as previously described¹.

Risk factors for seroconversion (SC) for HCV

All data of risk factors for HCV were collected by using special questionnaire, including the sex, age, renal function, HBV marker, EPO, infection at hospital, history of CAPD and kidney transplantation, duration of dialysis, history of transfusion, ALT abnormality, dialyzer reused.
Dialysis and disinfection procedure
HD was performed using dialysis machines from Baxter, Fresenius. We used bicarbonate dialysis fluid (flow 500mL/min). Water quality and bacterial count were monitored regularly. HD patients have been dialyzed with Cuprophan, polysulfone or hemophan dialyzer. A strict chemical disinfection using Citrosteril, run at 85°C for 35min after each dialysis session, was adopted before using the machine for the next patient. It was hoped that both the high temperature bath and the low pH offered by Citrosteril would be enough to combat HCV. But our patients shared machines indiscriminately.

Statistical analysis
Results are expressed as mean±SEM as indicated. Unpaired Student’s t test, χ² and Fisher’s exact test were used. P values <0.05 were considered as significant.

RESULTS
Prevalence of HCV marker in June 1996
In June 1996, the total positivity of HCV marker (HCVM) was 59.7% (37/62), 27 patients (43.6%) were anti-HCVIgM positive, 29 (46.8%) anti-HCVIgG positive, 34 (54.8%) HCV RNA positive, 22 (35.5%) anti-HCVIgM, anti-HCVIgG and HCV RNA positive, 27 were anti-HCVIgM and HCV RNA positive, 22 were anti-HCVIgM and anti-HCVIgG positive, 26 anti-HCVIgG and HCV RNA positive, 34 patients at least one of anti-HCVIgM and anti-HCVIgG positive, 3 each were anti-HCVIgG positive or HCV RNA positive only.

Sixty-two patients were divided into two groups, GI: 43 HD patients with histories of transfusion, ALT abnormality, kidney transplantation and HBV markers positive; GII: 19 HD patients without the history and abnormality as those of GI. Comparison of detection of HCVM in GI and GII is shown in Table 1.

When comparing the clinical manifestation between HCVM positive and negative groups, no significant differences were found with respect to the sex, age, renal function, HBV marker, EPO and history of CAPD and kidney transplantation; but there were significant differences in the duration of dialysis and ALT abnormality (Table 5).

Positive prevalence of anti-HCV antibodies in consecutive six-month period
Positive prevalence of anti-HCV antibodies was found in six consecutive period of 6 months as shown in Table 6.

Adequacy of serologic follow-up
Out of 346 patients followed up from June 1995 to December 1997, 48 did not complete the study as a result of death (n=22), kidney transplantation (n=24), transfer to other dialysis units (n=1), and transfer to peritoneal dialysis (n=1).

Incidence of SC for HCV
During the follow-up period (1-30 months), 80 patients had seroconversion (SC) for anti-HCV positive; 298, 167, 87, 48 and 11 were followed up for 6, 12, 18, 24, and 30 months; and their positive seroconversion rates were 6.4%, 11.9%, 20.7%, 35.4% and 54.5%, respectively. Of the 80 seroconverted patients, 57 patients had histories of transfusion, mean number of transfusion being 12.5U±6.2U.

ALT level in seroconverted patients
ALT determinations obtained every one month from the onset of HD were reviewed in 23 (28.8%) patients with SC. SC was preceded (1 to 6 months) by an unexplained, sustained (5 cases) or interrupted (18 cases) elevation of ALT level. This rise was not accounted for by hepatitis B virus infection or hepatotoxic drugs, and was noted for the first time since the initiation of HD. During the follow-up period, 4 patients had liver cirrhosis, 8, 3, 4 and 5 months after HD, respectively. 1 died after SC for 10 months, others remained in our HD center.
**Serologic follow-up of seroconverted patients**

All 80 seroconverted patients remained positive throughout the follow-up.

### Table 1: Comparison of detection of HCV in GI and GII

| Parameter                  | GI(%) (n=43) | GII(%) (n=19) | P value |
|----------------------------|--------------|---------------|---------|
| anti-HCV IgM (+)           | 21 (48.8)    | 6 (31.6)      | <0.05   |
| anti-HCV IgG (+)           | 25 (58.1)    | 4 (21.1)      | <0.05   |
| HCV RNA (+)                | 27 (62.8)    | 7 (36.8)      | <0.05   |
| All three (+)              | 18 (41.9)    | 4 (21.1)      | <0.05   |
| At least one (+)           | 29 (67.4)    | 8 (42.2)      | <0.05   |

### Table 2: Comparison of clinical manifestation in HCV positive and negative group of HD patients

| Parameter                  | HCV positive group (n=37) | HCV negative group (n=25) | P value |
|----------------------------|---------------------------|---------------------------|---------|
| MF                         | 22/15                     | 16/9                      | <0.05   |
| Mean age (years)           | 49.6±16.8                 | 48.4±14.4                 | <0.05   |
| Range                      | 16-71                     | 26-67                     |         |
| Mean duration of HD (months) | 31.2±8.6                 | 8.1±4.7                   | <0.01   |
| Range                      | 2-96                      | 1-24                      |         |
| History of transfusion     | 29 (78.4%)                | 11 (44.0%)                | <0.01   |
| EPO                        | 12 (32.4%)                | 8 (32.0%)                 | <0.05   |
| History of kidney          | 6 (16.2%)                 | 0 (0.0%)                  | <0.05   |
| transplantation(n=6)       |                           |                           |         |
| History of CAPD (n=8)      | 6 (16.2%)                 | 2 (8.0%)                  | <0.05   |
| HBV M positive             | 18 (48.6%)                | 10 (40.0%)                | <0.01   |
| ALT abnormality            | 10 (27.0%)                | 1 (4.0%)                  | <0.01   |
| BUN (mmol/L)               | 24.6±8.6                  | 28.4±10.2                 | >0.05   |
| Cr (µmol/L)                | 1154.4±402.6              | 1164.8±468.5              | >0.05   |

### Table 3: Relationship between dialysis times and HCV markers

| HD time (Year) | IgM | IgG | HCV RNA | Only one marker positive |
|----------------|-----|-----|---------|--------------------------|
| <1             | n   | n   | n       | n                        |
| 1-2            | 18  | 9   | 50.0    | 12 (61.1)                |
| 2-3            | 5   | 3   | 60.0    | 4 (80.0)                 |
| >3             | 7   | 6   | 85.7    | 7 (100.0)                |

### Table 4: Relationship between number of transfusion and HCV markers

| Transfusion (U) | IgM | IgG | HCV RNA | Only one marker positive |
|-----------------|-----|-----|---------|--------------------------|
| 0               | n   | n   | n       | n                        |
| 1-5             | 22  | 6   | 27.3    | 6 (27.3)                 |
| 6-10            | 16  | 7   | 43.8    | 6 (43.8)                 |
| 11-20           | 6   | 4   | 66.7    | 5 (83.3)                 |
| >30             | 10  | 8   | 80.0    | 9 (90.0)                 |

### Table 5: Comparison of the clinical manifestation between HCV positive and negative group in 22 patients without transfusion

| Clinical manifestation | Positive group | Negative group | P value |
|------------------------|----------------|----------------|---------|
| Cases                  | 8              | 14             | <0.05   |
| MF                     | 5/3            | 8/6            | <0.05   |
| Mean age (Years)       | 53±1±14.2      | 49±8±12.5      | <0.05   |
| Range                  | 30-71          | 30-67          |         |
| Mean duration of HD (months) | 24±2±6.4    | 3±4±1.6        | <0.01   |
| Range                  | 4±3±6          | 1±6            |         |
| History of kidney transplantation | 0          | 0              |         |
| History of CAPD        | 0              | 0              |         |
| EPO                    | 3              | 5              | <0.05   |
| ALT abnormality        | 3              | 1              | <0.05   |
| BUN (mmol/L)           | 25±7±8        | 26±4±6.8       | <0.05   |
| Cr (µmol/L)            | 1132±6±482.6  | 1182±4±464.3   | >0.05   |

### Table 6: Positive prevalence of anti-HCV antibodies in six consecutive periods of 6 months

| Time          | Cases | Positive (%) | Negative (%) |
|---------------|-------|--------------|--------------|
| 1995.6-1995.11 | 42    | 2 (4.8)      | 40 (95.2)    |
| 1995.12-1996.5 | 39    | 1 (2.6)      | 38 (97.4)    |
| 1996.6-1996.11 | 45    | 3 (6.7)      | 42 (93.3)    |
| 1996.12-1997.5 | 65    | 3 (4.6)      | 62 (95.4)    |
| 1997.6-1997.11 | 71    | 2 (2.8)      | 20 (97.2)    |
| 1997.12       | 21    | 0 (0.0)      | 21 (100.0)   |

### Table 7: Positive prevalence of anti-HCV antibodies in uremic patients when they were admitted to our HD center

| Time          | New patient | Positive (%) | Negative (%) |
|---------------|-------------|--------------|--------------|
| 1995.6-1995.11 | 42           | 2 (4.8)      | 40 (95.2)    |
| 1995.12-1996.5 | 39           | 1 (2.6)      | 38 (97.4)    |
| 1996.6-1996.11 | 45           | 3 (6.7)      | 42 (93.3)    |
| 1996.12-1997.5 | 65           | 3 (4.6)      | 62 (95.4)    |
| 1997.6-1997.11 | 71           | 2 (2.8)      | 20 (97.2)    |
| 1997.12       | 21           | 0 (0.0)      | 21 (100.0)   |

### DISCUSSION

Non-A, non-B hepatitis is a major worldwide health problem. It accounts for more than 90% of transfusion associated hepatitis cases[22] and was associated with a high incidence of chronic carrier state and subsequently progressive liver disease[7,21]. In 1989, HCV was isolated from most cases of blood-borne non-A, non-B hepatitis by Choo et al[36], the HCV was considered as the major cause of such disease, and HCV has evoked great interest, a plethora of reports have appeared in the literature for HD patients. Different prevalence rates of anti-HCV have been reported from different countries and the reported rates varied from as low as 3.3% in New Zealand[14], 39% in South America[6], 44%-60% in the Far-Eastern countries[29] to as high as 80.0% in Egypt[16]. By contrast, the country-wide anti-HCV prevalence among volunteer blood donors is 8.6±%[13]. Our results showed that the positivity of anti-HCV IgM was 43.6% (27/62), anti-HCV IgG 46.8% (29/62) and HCV RNA 54.8% (34/62), the total positivity was 59.7% (37/62). By excluding the HD patients with histories of transfusion, ALT abnormality, history of kidney transplantation and positive HBV markers, the positivity of HCV viremic was 42.2% (8/19). So HCV infection in our HD center is a very serious problem.

Our findings that 3 HD patients had detectable serum HCV RNA despite their anti-HCV negativity confirms previous observations, although figures vary considerably, ranging from 1% to 15%[3,4,37]. Fernandez et al[37] reported that 53 anti-HCV negative blood donors were examined for HCV RNA, and within the study group 4 patients (12.9%) were HCV RNA positive. The existence of HCV viremia without specific antibody expression in HD patients differs significantly when compared with blood donors who represent a control population. One explanation to account for the difference is that HCV RNA positivity precedes anti-HCV SC in an acute infection[3]. Another possible explanation is that the immunosuppression...
that characterizes HD patients may be responsible for the inability to express detectable amount of serum anti-HCV in the same way as is observed in kidney and liver transplantation recipients[19,38]. Therefore, detection of HCV RNA can improve positivity of HCV infection, as the compensation of inadequacy of anti-HCV.

Prospective studies of HCV infection in HD patients were fewer and the conclusions were not consistent[8,22,29,32-34,39]. Dentico et al[11] using a less sensitive ELISA I test reported in 115 Italian HD patients, a yearly incidence of SC for HCV falling from 6.1% to 2.2% between 1984 and 1990. Two small prospective studies relying on the ELISA I test in 35 and 62 HD patients followed for 12 and 18 months, reported a yearly incidence of 11.4%[23] and 6%,[40] respectively. Chan et al[9] using ELISA II test prospectively reported a yearly incidence of 4.9% in 39 HD patients followed for 19 months. Jadoul et al[28] reported prospectively the SC for HCV in 401 HD patients, the SC rate averages 1.7% per year. More recently, in a prospective study relying on the ELISA II test in 187 HD patients followed for 36mo, a yearly incidence of SC for HCV was 22.6%[29]. Our study defined prospectively the SC using the sensitive ELISA II in a large series of 346 HD patients. During the 1-30 months follow-up period, a total of 80 patients had SC for anti-HCV positive; 298, 167, 87, 48 and 11 patients were followed up for 6, 12, 18, 24, and 30 months; their positive SC was 6.4%, 11.9%, 20.7%, 35.4% and 54.5%, respectively.

Our study confirms that blood transfusion is an important risk factor for the transmission of HCV in HD patients. We have demonstrated a positive correlation between the two which increased with the increase in the number of transfusion units. Similar results have been reported by many other investigators.[11,2,8,9,12,15,19,21-23,31] In addition, the introduction of screening of blood products for anti-HCV has led to a decline in the incidence of post-transfusion hepatitis[34].

However, factors other than transfusion contribute to the transfecion of HCV as demonstrated by the absence of blood transfusion in 23 of the 80 patients with SC. Interestingly, other studies have detected HCV antibodies in up to 19%-39% of HD patients who never received blood transfusion[9,23,41]. The span of dialysis was significantly longer in anti-HCV positive patients than in anti-HCV negative patients[11,5,12,19,25,31]. The risk of acquiring HCV infection on HD has been estimated to be 10% per year[29]. These facts raised the possibility of nosocomial transmission. This hypothesis is supported by our observations that patients dialyzed in a bed adjacent to that of an anti-HCV positive patients had significantly higher risk of SC than the others in our unit[11,8,12,14,25,31]. But until recently, the route of nosocomial transmission is not very clear. Transmission of infection to dialysis staff by needle-stick injury[11,25,26], breakdown in standard infection control practices[11,23,26,28,42,43], physical proximity to an infected patient[1,8,25,28] through dialysis machines[1,25,26], dialyzer membranes[44], hemodialysis ultrafiltrate[13,44] and reprocessing of dialyzers[14,19] implicated a variety of potential modes of HCV transmission.

Several studies advocated the segregation of HCV (+) from HCV (-) patients to prevent nosocomial transmission[9,22,25,29]. Implementation of a rigorous separation between patients according to their HCV status is rather cumbersome. Also in treating HBV positive patients, this would imply up to four separate facitities (B+C+, B+C-, B-C+ and B-C-). However, there are strong arguments against a policy of isolating anti-HCV positive patients because: HCV is not as infective as HBV, circulates in low titer in infected serum and is rapidly degraded at room temperature[45]; and Currently licenced anti-HCV test detects non-neutralizing antibodies, does not distinguish between current and post infection, and a negative test does not exclude HCV infection[42]; although isolation may protect uninfected patients, it might also increase the risk of superinfection in patients originally infected with a single strain[46]. Infection with two or more different HCV genotypes has been observed in HD patients and 13% of patients referred for renal transplantation[47]. Grouping of anti-HCV positive patients in dialysis units might thus increase their risk acquiring multiple HCV strains.

In view of the above debate, the centers for Disease Control and Prevention in the U.S. (CDC) recommend dedicated machines, patient isolation or a ban on reuse in HD patients with HCV infection[38,49]. Such measures are detailed in the universal precautions for prevention of transmission of blood borne pathogens in health care setting[47,49] and recommended precautions for patients undergoing hemodialysis who have AIDS or non-A non-B hepatitis delineated by the CDC[48]. They include cleaning and disinfection of instruments, machines and environmental surfaces that are routinely touched, avoidance of sharing of articles between patients, frequent handwashing and use of glove.

In conclusion, the status of HCV infection in HD patients was a very serious problem, contamination appears to be both transfusion and nosocomial. Strict adhesion to the ‘CDC guidelines’ and isolation of HCV positive patients during dialysis sessions are recommended. Further long-term studies are needed to confirm these conclusions.

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