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Full Length Research Paper

Hepatitis C virus infection in uremic patients on maintenance hemodialysis: A follow up study for 150 months

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We aimed to delineate the incidence of hepatitis C virus (HCV) infection and HCV seroconversion (SC) in maintenance hemodialysis (HD) patients and to evaluate the effect of isolation measures on HCV in HD unit. From June 1998 to June 2010, 2465 maintenance HD patients in our HD unit were enrolled in, and the anti-HCV ELISA and HCV nucleic acid testing were consecutively performed every six months. The results showed the prevalence rates of HCV antibody detected consecutively every six months were 54.7, 53.8, 52.6, 53.0 , 51.2, 45.9, 45.5 and 48.2% before 2002 (without isolation measures) and 35.6, 33.7, 33.7, 31.7, 30.4, 28.4, 27.2, 24.5, 20.8, 19.4, 16.6, 14.4, 15.3, 15.2, 12.5, 11.9 and 10.0% since 2002 (with isolation measures), respectively. HCV SC occurred in 238 patients during the follow-up period. 1077 patients were followed for 1 to 12 months, of which 49 (4.5%) had SC for HCV. The SC rate increased to 75% in 8 patients followed for 139 to 150 months. Taken together, we conclude that the dialysis environment is responsible for transmission of HCV either due to common usage of the machines or to the fact that the HCV positive patients are not isolated. The application of isolated hemodialysis of anti-HCV positive patients plus strict supervised universal infection control techniques significantly effect on the long-term prevalence of HCV antibody and SC in HD patients.

Key words: Hemodialysis, hepatitis C virus, seroconversion, blood transfusion, nosocomial transmission.

INTRODUCTION

Hepatitis C virus (HCV) infection is a severe problem in maintenance hemodialysis patients. Patients infected with HCV are more susceptible to develop chronic hepatic diseases, hepatic cirrhosis and hepatocellular carcinoma than patients infected with hepatitis B virus (HBV) (Caramelo et al., 1993; Jadoul et al., 1993). Prevalence of HCV infection has decreased in patients on maintenance hemodialysis in recent years, but still remains a significant public health concern (Espinosa et al., 2004). Currently, there is no special and effective radical therapy for HCV and the treatment fees are substantially high. Therefore, the most important thing is to prevent HCV infection. However, most studies of HCV infection in maintenance hemodialysis patients are cross-sectional, and neither overseas nor domestic long-term follow-up studies are sufficient and their conclusions are quite inconsistent (Donahue et al., 1992; Espinosa et al., 2004; Souqiyyeh et al., 1995; Wang et al., 2000).

Patients on hemodialysis are at particular high risk for blood-borne infections because of prolonged vascular access and potential for exposure to contaminated equipment. It has been estimated that, among patients on hemodialysis, the prevalence of HCV infection varies greatly, from less than 5% to nearly 60% according to different areas of the world (Perico et al., 2009). Given the introduction of routine screening and heightened attention to prevention of HCV spread, the prevalence of HCV infection has declined in many dialysis centers, and yet remains unacceptably high, ranging from 8 to 10% even in the most industrialized countries (Meyers et al., 2003). The presence of anti-HCV antibodies may be an

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independent and significant risk factor for death, mainly resulting from increased incidence of liver cirrhosis and hepatocellular carcinoma. Analysis of the American database of more than 13000 maintenance hemodialysis patients has shown that HCV infected patients have a higher all-cause and cardiovascular mortality across almost all clinical, demographic, and laboratory groups than HCV-negative subjects (Kalantar-Zadeh et al., 2007).

We once reported a 30-month follow-up study in hemodialysis patients with HCV infection and found that HCV infection was very common in this special population (Wang et al., 2000). Herein we conducted a 150-month long-term follow up study in such patients. The aims of this study were: (1) to determine the prevalence of hepatitis C virus (HCV) infection and the seroconversion (SC, which means convert from a HCV negative state to a HCV positive state.) in our HD unit by serology and NATs further; (2) to investigate whether an isolated hemodialysis mode reduces the incidence of HCV infection.

MATERIALS AND METHODS

Case recruitment

This study was conducted from June 1998 to November 2010 for consecutive150 months. All the cases were patients underwent maintenance hemodialysis from outpatient and or ward of our hospital and the patients infected with Hepatitis B Virus (HBV) were excluded from this study. Among the 2465 patients enrolled in, 1172 did not receive any hemodialysis before, 32 received hemodialysis before and came here due to kidney transplantation failure, and 59 were transferred from other units with hemodialysis histories.

Specimen collection and HCV tests

HCV tests were conducted for all patients every six months. Detection of anti-HCV antibodies was performed by using enzyme immunoassay. It allows rare false-negative results in dialysis patients but does not distinguish acute and chronic HCV infection. Therefore, in enzyme immunoassay-positive patients, HCV infection was further confirmed by HCV RNA assay in a blood sample. Venous blood samples for HCV test were drawn from all the patients before initiation of hemodialysis to avoid false-positive PCR results caused by the presence of heparin in the blood (Perico et al., 2009). Hepatic and renal functions, electrolyte and blood routine were regularly followed up monthly, and serum samples for anti-HCV test were collected every six months. These blood samples were separated into three aliquots, one for serological tests, the other for PCR and the third reserved for any necessary result confirmation. The sera aliquots were stored at –20°C and –80°C, respectively. Anti-HCV tests (ORTHO® HCV Version 3.0 ELISA Test System) and NATs were conducted regularly by a particular professional staff with versed technique in the same laboratory for all patients. The presence of HCV-RNA in plasma was established by nested RT-PCR as described previously (Jadoul et al., 1998). In each reaction set, water samples were used as negative controls to exclude possible cross contaminations due to amplicon carry-over. Only those being positive both in ELISA and NAT were considered as HCV positive.

Data collection

A dedicated survey form was used to record data including transfusion history, transfusion frequency and volume of blood products, time of hemodialysis, nosocomial infection, hepatic and renal function, EPO application, kidney transplantation, etc.

Sterilization and isolation measures

Hemodialysis was performed using dialysis machines from Baxter, Fresenius. Water quality and bacterial count were monitored regularly. Hemodialysis systems were disinfected as the manufacturers instructed. The external surfaces of dialysis machines, dialysis bed or chair, countertops, and equipment including scissors, hemostats, clamps, blood pressure cuffs, stethoscopes, chart files and utility carts were disinfected regularly with the disinfectant. Fistula needles were designed for single use; reusable pipelines were sterilized rigorously by chemical methods according to the standard operation procedure. Ozone was used for indoor air sterilization. Staffs were required to wash their hands with an antiseptic and water, before and after contact with a patient or any equipment at the dialysis station. Disposable gloves were necessary when caring for a patient or touching any potentially contaminated surfaces and the gloves were removed promptly after use. Patients were also suggested to clean their hands, or use an alcohol gel rub, when arriving at and leaving the dialysis station.

The study was divided into two stages according to chronology (before 2002 and after 2002, respectively). The patients shared machines indiscriminately before 2002 (stage 1). Since 2002 (stage 2), the HCV positive hemodialysis patients were isolated and underwent dialysis in positive dialysis unit and the others in negative dialysis unit. The nurses were allocated specifically to the negative and positive HD units respectively and no nurses were allowed to cover both units thereafter. The dressing rooms were also independent. In the emergency room, positive and negative patients were not treated simultaneously, and there were machines specifically assigned to either positive or negative patients. The patients with an uncertain serological status were presumed to be HCV negative and dialyzed in emergency room if an urgent hemodialysis was needed. In such a case, the used dialysis machine was temporally suspended until the serological results were available as soon as possible. Medications and other supplies were not allowed to be moved between patients. There was no difference in sterilization techniques of HD machines and dialysis rooms before and after isolation.

Statistical analysis

SPSS for Windows software, version 13.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Student t test was used to compare means between two groups, $\chi 2$ test was used to analyze the incidences or infection rates, and a P value below 0.05 was considered statistically significant.

RESULTS

HCV test results obtained every six months

HCV test results obtained every six months were presented in detail (Figure 1). The prevalence rates of HCV antibody were 54.7, 53.8, 52.6, 53.0, 51.2, 45.9, 45.5 and 48.2% before 2002 (without isolation measures) and 35.6, 33.7, 33.7, 31.7, 30.4, 28.4, 27.2, 24.5, 20.8%,

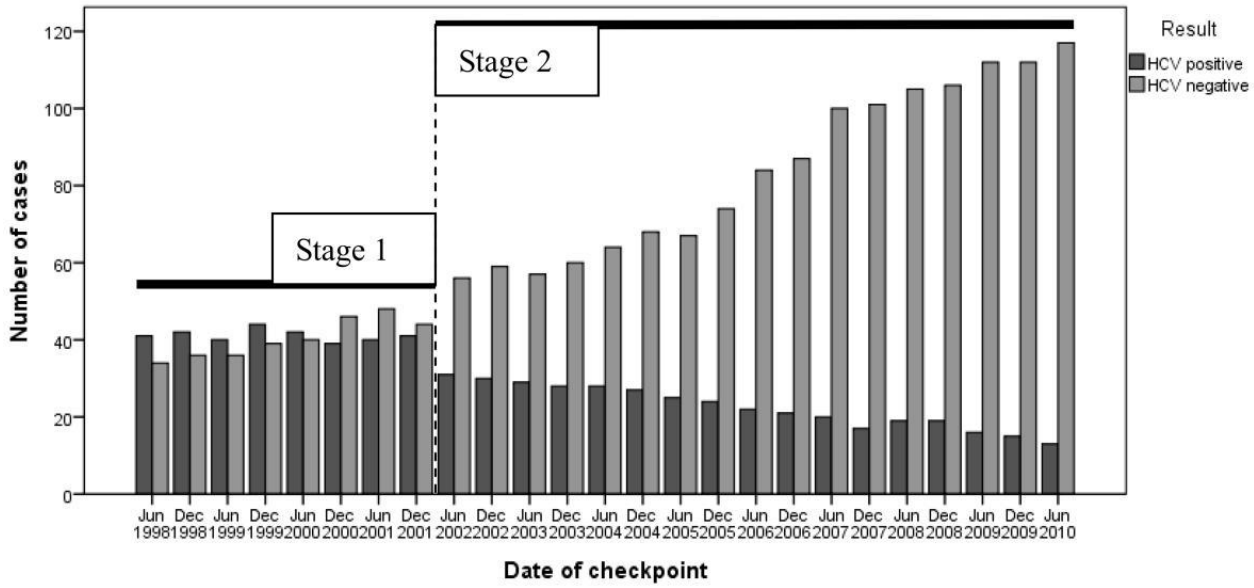

Figure 1. HCV test results in maintenance hemodialysis patients obtained every six months.

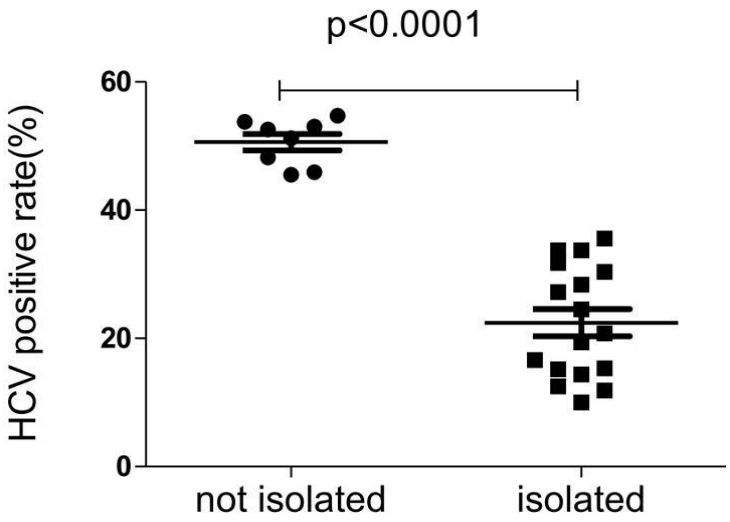

Figure 2. HCV positive rates in patients in stage 1 (not isolated) and stage 2 (isolated).

19.4, 16.6, 14.4, 15.3, 15.2, 12.5, 11.9 and 10.0% since 2002 (with isolation measures), respectively. Total HCV positive rate obtained every six months remained high and HCV infection rate also kept high in stage 1 though the rigorous sterilization and preventive measures were adopted. No difference was found in the HCV positive rates during this period ($\chi 2 = 3.030$, $P = 0.822$). The HCV positive rates in stage 2 (since June 2002) decreased significantly ($\chi 2 = 75.973$, $P < 0.001$). As a result, HCV positive rate in June 2010 reduced to 10.0% only. The mean HCV positive rates were also significantly different in those two periods (Figure 2. $t = 8.708$, $p < 0.0001$).

HCV positive rates of uremic patients before hemodialysis

During the whole period of study, a total of 1263 new uremic patients came to our unit for dialysis, and 40 (3.2%) cases were detected HCV positive (Table 1). In those HCV positive cases, 11 had a history of kidney transplantation, 12 were transferred from other units for kidney transplantation, and all these patients had a history of hemodialysis; only 17 (1.3%) patients undergoing hemodialysis for the first time were proved HCV positive.

Table 1. HCV positive results in new uremic patients in our HD unit.

Chronology	Number of new cases	Number of HCV positive cases (%)	Number of HCV negative cases (%)
Jun 1998-Nov 1998	45	2 (4.4)	43 (95.6)
Dec 1998-May 1999	43	1 (2.3)	42 (97.7)
Jun 1999-Nov 1999	48	3 (6.3)	45 (93.7)
Dec 1999-May 2000	49	2 (4.1)	47 (95.9)
Jun 2000-Nov 2000	52	3(5.8)	49 (94.2)
Dec2000-May 2001	55	3 (5.5)	52 (94.5)
Jun 2001-Nov 2001	61	2 (3.3)	59 (96.7)
Dec 2001-May 2002	41	0 (0.0)	41 (100.0)
Jun 2002-Nov 2002	45	1 (2.2)	44 (97.8)
Dec 2002-May 2003	43	2 (2.4)	41 (97.6)
Jun 2003-Nov 2003	58	1 (1.7)	57 (98.3)
Dec 2003-May 2004	55	2 (3.6)	53 (96.4)
Jun 2004-Nov 2004	64	2 (3.1)	62 (96.9)
Dec 2004-May 2005	56	2 (3.6)	54 (96.4)
Jun 2005-Nov 2005	47	1 (2.1)	46 (97.9)
Dec 2005-May 2006	53	3 (5.7)	50 (94.3)
Jun 2006-Nov 2006	54	2(3.7)	52 (96.3)
Dec 2006-May 2007	47	2 (4.3)	45 (95.7)
Jun 2007-Nov 2007	62	1 (1.6)	61 (98.4)
Dec 2007-May 2008	45	2 (4.4)	43 (95.6)
Jun 2008-Nov 2008	43	1 (2.3)	42 (97.7)
Dec 2008-May 2009	48	0 (0.0)	48 (100.0)
Jun 2009-Nov 2009	52	1 (1.9)	51 (98.1)
Dec 2009-May 2010	46	1 (2.2)	45 (97.8)
Jun 2010-Nov 2010	51	0 (0.0)	51 (100.0)
Total	1263	40 (3.2)	1223 (96.8)

Seroconversion for HCV in hemodialysis patients during follow-up

Among 2465 patients received HCV test, 2019 cases (excluding 81 HCV positive cases at the entry of the study and 365 cases withdrew from the study) were followed up for 1 to 150 months and seroconversions were found in 238 cases. In those patients with SC, 177 cases had blood or blood products transfusion history with a mean volume of 6.5 ± 2.2 U but the other 61 had not been transfused at all (Figure 3). A total of 1077 patients were followed for 1 to 12 months, of which only 49(4.5%) had SC for HCV. The SC rate increased in parallel with the total duration of hemodialysis or time of follow up (Table 2). As indicated in Table 2, there were 8 patients were followed for 139 to 150 months, and the SC rate for HCV in those patients reached the tremendous 75.0%.

Hepatic function changes and prognosis of patients with SC during follow-up

During the follow-up period, 64 of 238 (26.9%) hemodialysis patients with SC had elevated ALT levels discontinuously and 9 (3.78%) had increased ALT levels persistently, 8 (3.36%) patients finally developed hepatic cirrhosis and 1 (0.42%) patient developed hepatocellular carcinoma. Two patients (0.84%) died due to gastrointestinal bleeding combined with hepatic coma or extensive metastasis of tumor cells complicated with gastrointestinal bleeding.

DISCUSSION

HCV infection represents a major medical and epidemiologic challenge in patients with end-stage renal disease on renal replacement therapy with dialysis or transplantation. Currently, reports focused on the prospective studies of maintenance hemodialysis patients with HCV infection are rare and the conclusions are inconsistent. Jadoul et al (1993) followed up 401 hemodialysis patients for 18 months, using the ELISA method to detect HCV antibodies, found that mean SC rate for HCV was 1.7%, only eight cases showed SC during follow-up, and total HCV positive rate was 13.4%. Souqiyyeh et al (1995) conducted a multicenter, 21-month follow-up study which indicated an annual HCV positive rate of 7 to 9%. We (Wang et al., 2000) once followed up the hemodialysis patients in our HD unit and 80 patients seroconverted during the follow-up of 1 to 30

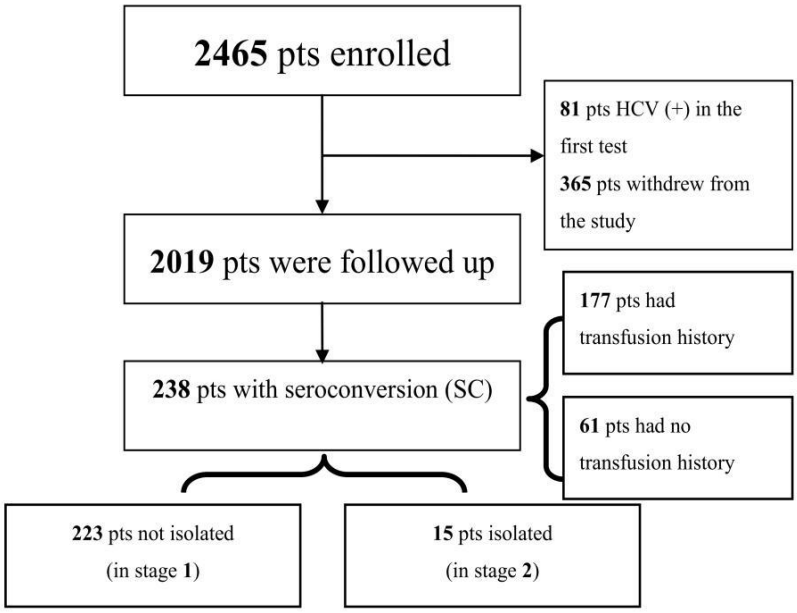

Figure 3. Algorithms of patients in follow-up study.

Table 2. Seroconversion (SC) for HCV in hemodialysis patients during follow-up.

Duration of follow up (months)	Patients followed up	Patients with SC	SC rate (%)
1-12	1077	49	4.5
13-24	421	29	6.9
25-48	196	35	17.9
49-60	114	32	28.1
61-72	77	27	35.1
73-84	57	22	38.6
85-96	32	15	46.9
97-108	16	9	56.3
109-126	11	7	63.6
127-138	10	7	70.0
139-150	8	6	75.0

months. This variance may be explained by the different standards of application, the adherence to infection-control policies and procedures, and the isolation policy of machines and patients among different HD units.

Our present data demonstrated that HCV infection was still a severe problem in the HD unit, especially in those on dialysis for a considerable long time. Those findings were consistent with the conclusions that the duration of HD was a risk factor for HCV infection (Hardy et al., 1992).

Our results showed that the HCV positive rate in new uremic patients before hemodialysis in our HD unit was approximately 3.2%. This indicated that the HCV positive rate in new uremic patients before hemodialysis was similar with that in general population, as documented before (Donahue et al., 1992). From June 1998 to December 2001(stage 1), the HCV infection rates in hemodialysis patients remained high though the rigorous sterilization and preventive measures were adopted. This was consistent with the results reported by Abu-Aisha (1995). Since June 2002, the HCV positive rates decreased significantly, indicating that the isolation together with rigorous sterilization measures effectively prevented the infection and transmission of HCV in hemodialysis patients.

Hemodialysis centers are well-recognized venues for hepatitis virus transmission for there existed abundant opportunities of contamination of the environment and equipment (Petrosillo et al., 2001; Thompson et al., 2009). Nosocomial routes of transmission including the

use of contaminated equipment and patient-to-patient exposure are considered important.

Several prophylactic measures have been suggested to avoid infection by HCV in the HD environment (Alavian, 2009). Many HD centers have improved their adherence to infection-control policies and procedures, and some have even applied the isolation policy of infected HD machines and patients. Some investigators have suggested a decline in HCV prevalence among HD patients in recent years, mostly attributable to strict adherence to universal precautions with observing isolation measures (Agarwal et al., 2009; Barril et al., 2003; Carneiro et al., 2005; Gallego et al., 2006; Harmankaya et al., 2002; Jadoul et al., 2004; Saxena et al., 2003; Saxena et al., 2002; Shamshirsaz et al., 2004; Taskapan et al., 2001; Yang et al., 2003).

Detection of anti-HCV antibodies by ELISA allows rare false-negative results in dialysis patients but does not distinguish acute and chronic HCV-infection (Souqiyyeh et al., 1995). Additionally, in enzyme immunoassay-positive patients, HCV infection should be confirmed by NATs in a blood sample. Quantitative determination of viral load is also useful to provide prognostic information about the infection.

With promotion of HCV test among blood donors and wide application of erythropoietin (EPO), HCV infection associated with transfusion has been decreased greatly; meanwhile, dialysis environment-related nosocomial HCV transmission is attracting more and more attention. Our results indicated that nosocomial HCV transmission was associated with dialysis environment, or sharing one dialysis machine, or always placing dialyzers in a same dialysis unit. Therefore, besides stringent sterilization and preventive measures, strict isolation measures should also be applied, and HCV positive patients should be separated and dialyzed individually. The Quality Management Center of Hemodialysis in Shanghai region has proposed sub area and isolation of dialysis as an important part of quality management, and normalized the preventive measures against HCV infection in hemodialysis patients.

In some countries, both prevalence and incidence of HCV infection remain very high, and nosocomial transmission are partially responsible at least, probably due to the gap between limited resources available and a rapidly growing HD population to treat (Rutkowski, 2000; Vladutiu et al., 2000). A genuine transmission could be caused by the leakage of blood or blood components through the dialysis filter. Alterations in pore size and microfractures of the membrane are possible events in the course of manufacturing, during the dialysis session or with dialyzer reuse. So HCV transmission may be acquired through sharing a hemodialysis machine (Karkar, 2011; Thomson et al., 2011). A second type of contamination is caused by occasional or systematic contaminations of machine and instruments (Sampietro et al., 1996).

Separating dialysis machines and infected patients, keeping infection-control policies and procedures strictly and training of nursing staff regularly were proved particularly usable in prevention and control of the HCV dissemination in dialysis units (Karkar, 2007). One study assessed the characteristics and outcomes of HCV infections among patients undergoing regular HD in a small dialysis centre in Singapore and found that HCV infection was common among patients attending HD and sharing of dialysis machines was an important factor (Chong and Zinna, 2008).

In our study, an excellent use of universal precautions was observed as well as the fact that the HCV positive and HCV negative patients were placed in separate rooms. Meticulous practice of preventive measures is essential to eradicate the spread of HCV in HD units. Our study also has limitations for we tested anti-HCV mainly based on ELISA and then utilized NAT only in ELISA positive samples. However, we know that ELISA has a false-positive or false-negative rate and it cannot detect HCV infection in its' early stage. It was estimated once that HCV viraemia was present in more than 90% of the anti-HCV positive patients and none of the anti-HCV negative patients were shown to be viraemic by NATs (Albuquerque et al., 2005). So some infected patients may not be distinguished promptly and the incidence of infection may be underestimated.

Dissidences still exist (Abboud et al., 2008; Aucella et al., 2000; dos Santos et al., 1996; Jadoul et al., 1998; Karkar et al., 2006; Valtuille et al., 2002). There is no consensus on the necessity for isolation of HCV-positive patients for at least two reasons: firstly, the infectivity of HCV is lower than that of the hepatitis B virus; secondly, the criteria for patients to be isolated remains to be defined for some HD patients are infected with HCV but do not have anti-bodies. Detection of viral RNA by reverse-transcription polymerase chain reaction (RT-PCR) is the only method to confirm HCV infection but this technique is not available at all centers, especially in developing countries.

In conclusion, HCV infection is highly prevalent among patients on hemodialysis and it increases morbidities and mortalities in this special population. Blood transfusions, times of dialysis and nosocomial routes of transmission including the use of contaminated equipment and patient-to-patient exposure are considered of importance in HCV spread in HD unit. Dialysis on isolated machine placed in separated room combined with rigorous sterilization measures can effectively prevent the infection and transmission of HCV in HD units, especially in HCV high prevalence regions.

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