

# EPIDEMIOLOGY AND RISK FACTORS FOR HEPATITIS C VIRUS INFECTION IN PATIENTS WITH END STAGE RENAL DISEASE ON MAINTENANCE DIALYSIS

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## REZUMAT

Infecția cu virusul hepatitic C (VHC) rămâne o mare problemă de sănătate pe plan mondial, datorită incidenței în continuă creștere. Cu atât mai mult, la persoanele cu risc crescut - cum sunt pacienții hemodializați - infecția cu VHC este foarte frecventă, dar dificil de diagnosticat și tratat. Din acest motiv este foarte important să fie identificate căile de infectare și de transmitere a VHC în cadrul acestui grup de bolnavi, pentru a putea controla numărul mare de infecții cu HCV la bolnavii dializați.

**Cuvinte cheie:** dializă, VHC, epidemiologie

## ABSTRACT

The worldwide incidence, prevalence and risk factors of hepatitis virus (HCV) infection is very well known, offering a worrisome perspective regarding the potential effects of this infection in the very next future. In high risk patients - such as patients with end stage renal disease in dialysis program - the HCV prevalence is much, much higher, posing difficult problems regarding diagnosis and treatment. Knowing the difficulties in HCV diagnosis and treatment in those patients, it is very useful to understand the epidemiology, ways of infection and potential measures of its prevention, in order to reduce the risk of infection.

**Key Words:** dialysis, HCV infection, epidemiology

## INTRODUCTION

The HCV infection prevalence varies worldwide. The highest number of HCV infections has been reported in Egypt (6-28%), due to the antischistostoma therapy. In USA, the reported anti-HCV prevalence is 1,8%, representing 4.000.000 persons, out of which 2.700.000 persons have detectable HCV-RNA.<sup>1</sup>

The proportion of HCV infections detected in blood donors does not imply the same level of proportion in the general population, mainly because the blood donors are highly selected persons, with a serious screening of potential risk factors for viral hepatitis. In the US, the HCV prevalence in general population is about 6 times higher than the prevalence observed in blood donors, ie 1.8%.<sup>1</sup> Similar results were observed in other studies around the world, including Africa, Middle East and the Mediterranean countries; for example, in Greece the HCV infection prevalence in the general population is 0.7-7.9%, 3-30 times higher than that determined in blood donors.<sup>4</sup>

In Romania, such a populational study does not really exist. The HCV prevalence was estimated basically from studies performed in patients admitted in liver units, and from the screening results from blood donors. The results are discouraging:

- The HCV prevalence in blood donors varies: 0.3-2.6%<sup>5,6</sup>

- WHO reports an anti-HCV prevalence of ~ 4.5% in the general population.<sup>7</sup>

The worldwide distribution of hepatitis C virus is well-known, including the prevalence and incidence of

**Table 1.** Prevalence of HCV infection in USA, Italy and France

Author, year	No.	Population	anti-HCV Prevalence	HCV-RNA Prevalence
Alter, 2000 <sup>1</sup>	21,241	NHANES III study	1.8%	1.3%
Bellentani, 1999 <sup>2</sup>	6,917	Dionysos study	2.6%	2.3%
Dubois, 1997 <sup>3</sup>	6,283	volunteers from 4 french counties	1.15%	0.93%

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chronic C hepatitis, especially in high risk populations, such as patients with end stage renal disease (ESRD) in hemodialysis program. Establishing the chronic C viral infection is often difficult, because the infection remains almost completely silent for very long period of time, reason to call the infection with HCV the “sleeping giant” or “bombe à retardement”.<sup>8,9</sup> This lack of symptoms or the vague nature of them is more difficult to interpret in patients with ESRD.

In patients with chronic decompensated renal failure there is always a more or less pronounced immunodepression, the latter being emphasized in patients treated by hemodialysis and blood transfusions, thus conducting to important deficiencies of the defense immune system, favoring – in these patients – bacterial and viral infections (i.e., hepatitis B and C viruses).<sup>10</sup>

## **DIAGNOSIS OF HCV INFECTION IN DIALYSED PATIENTS**

The problem of HCV infection diagnosis in dialysed patients is more complicated, first of all because of the discrepancy between serum ALT levels and the presence of anti-HCV, mainly due to the following reasons:

- chronic HCV infection characteristically has a fluctuating course in ALT levels;<sup>11</sup>
- some anti-HCV-positive patients may have cleared the infection and anti-HCV may be the remnant of past infection;
- baseline serum ALT levels are depressed in patients on dialysis.<sup>12</sup> However, elevated serum ALT has been observed in 4-23% of anti-HCV negative dialysis patients.<sup>11,13</sup>

There is very few data concerning the natural history of acute HCV infection in patients undergoing maintenance dialysis. A prospective study of 19 dialysis patients with acute infection found that, at a median follow-up of three years, nearly 80 % remained viremic.<sup>14</sup> In general, the greater the elevation in serum ALT, the higher the probability of histologic evidence of the liver disease in HCV infection. Among hemodialysis patients, this correlation is weak, serum ALT levels are elevated in: 4-67% patients with anti-HCV, 12-31% of patients with HCV-RNA, 1/3 of patients with biopsy-proven hepatitis.<sup>11,13</sup> Because of these limitations, liver biopsy remains the only reliable method of confirming the presence and assessing the severity of liver disease in patients with HCV infection. Liver histology at the time of initial presentation has been shown to be a good predictor of intermediate

and long term outcome in renal transplant recipients with liver disease.<sup>15</sup>

Another difficult issue in this high-risk group of patients is that the presence of anti-HCV does not necessarily imply the presence of HCV RNA in the serum. There are many possible explanations for this situation:<sup>11,13,16</sup>

- HCV may be sequestered at sites other than the blood stream, such as the liver or peripheral blood mononuclear cells;

- viremia could be intermittent and HCV-RNA may not be present in the plasma at the time of determination;<sup>17</sup>

- the number of copies of HCV RNA may be below the limit of detection;

- antibodies to HCV persist even after the viral RNA has disappeared, representing patients who had been infected with the virus, but are no longer infected;

- anti-HCV may have been passively acquired from blood transfusions;

- false positive results can occur due to nonspecific reactions, a problem which has been largely resolved with the use of ELISA in combination with RIBA;

The alternate situation is the anti-HCV negative and HCV-RNA positive patient, a situation requiring some possible explanations:

- the anti-HCV test may not be sensitive enough to detect existing anti-HCV antibody;

- various diseases or drug-induced immunosuppression could modify the anti-HCV response in dialysis patients; some studies are showing that only 83% of those who are HCV-RNA positive test positive for anti-HCV and 2.5-12% of those who are anti-HCV negative by first or second generation ELISA test positive for HCV RNA.<sup>11,13</sup> In one study, in an endemic area of HCV infection (Saudi Arabia), 28% of the hemodialysis patients, who were anti-HCV negative by third generation, ELISA tested positive for HCV-RNA;<sup>18</sup>

- the patient may be in the “window” period between infection and anti-HCV seroconversion;

- after anti-HCV antibody has persisted for a certain period of time, it can disappear despite the persistence of HCV-RNA.

In addition to the above possibilities, HCV-RNA has been detected in the peripheral blood mononuclear cells of hemodialysis patients without anti-HCV or HCV-RNA in the serum. The HCV-RNA in these cells could therefore serve as a viral reservoir and can further block further efforts to identify HCV infection.

Taking into account all the mentioned data, it seems

that the best but not perfect diagnostic tool of HCV infection in patients on dialysis is the determination of the viral level HCV-RNA by polymerase chain reaction (RT-PCR).

## **PREVALENCE OF HCV INFECTION IN DIALYSIS PATIENTS**

The prevalence of anti-HCV antibody among patients on dialysis is much higher than in healthy populations, suggesting that dialysis patients may be at higher risk of acquiring HCV infection. The incidence of HCV infection is declining in the developed countries, among member nations of the European Dialysis and Transplant Association (EDTA), for example, the prevalence of anti-HCV declined from 21% in 1992 to 17.7% in 1993. Nonetheless, the 0.4 to 15% incidence of anti-HCV in hemodialysis (HD) units continues to be a cause of concern.<sup>11</sup> The situation in Romania is completely different.

The reported incidence, however, varies based in part upon the type of laboratory assay used (ELISA3 > ELISA2 > ELISA1 in terms of sensitivity and specificity, respectively), observed the dialysis unit. In addition to the wide range in the prevalence of HCV infection among different countries, there is also a wide variation in the prevalence of HCV infection among dialysis units and the geographic regions within a single country.<sup>13,19-35</sup> Third generation anti-HCV tests (ELISA 3) are currently largely in use, with greater sensitivity and specificity compared to second generation tests (ELISA 2), although the incidence is declining, mainly because of the implementation of infection-control measures to prevent nosocomial transmission within dialysis units. (Table 2)

**Table 2.** Prevalence of anti-HCV in dialysis patients in different countries

Author	Contry	Year	Anti-HCV Prevalence	Reference
Fabrizi	Italy	1997	13,5-28%	22
Biamino		1999		23
Courouce	France	1995	42%	24
Covic	Romania	1999	75%	25
Natov	USA	1999	19%	26
De Medina				27
Othman	Syria	2001	49%	28
Rigopoulou	Greece	2005	36%	29
Khaja *	India	2005	37%	30
Reddy			10%	31
Kumagai *	Japan	2005	13%	32
Qadi	Bahrain	2004	9,2%	33

\* HCV-RNA testing

Nevertheless, the incidence and prevalence of HCV infection among patients on dialysis is steadily declining. This decline was initially due to the reduction in post-transfusion HCV infection; subsequently, it has reflected the implementation of infection-control measures to prevent nosocomial transmission within dialysis units.<sup>11</sup>

In Romania, during the last 10 years some studies have been published, giving a grim perspective about this infection in this high-risk group of patients: in one study, up to 78% of dialysed patients were anti-HCV positive, while another study showed a 92% of dialysed patients positive for anti-HCV.<sup>34-35</sup>

### **Risk factors for HCV infection in dialysis patients - transmission through blood transfusions and blood products**

Blood transfusion was a major risk for acute infection in the past, with more than 10% of transfusion recipients acquiring infection in some studies.<sup>13</sup> The initiation of donor screening for anti-HCV antibodies in 1990 has nearly eliminated the risk of posttransfusion acute HCV infection. The estimated risk is now 1:100,000, with the remaining small risk probably being due to recent acquisition of HCV infection by the donor prior to the appearance of anti-HCV antibodies – the “immune window” period, lasting usually 12 weeks.<sup>36</sup> Another blood donor HCV testing technology, nucleic acid testing (NAT), was introduced in 1999 and it is hoped that this technology, which detects HCV genetic material rather than later-appearing antibodies, will further decrease the risk of transfusion-transmitted HCV to a range between 1:500,000 and 1:1,000,000 units, a 5- to 10-fold reduction.<sup>37,38</sup>

Finally, careful selection of blood donors and the use of third generation anti-HCV tests (ELISA 3), in combination with the introduction of erythropoietin, will bring further down the prevalence of HCV infection in dialysis patients.

On the other hand, plasma products and concentrates of clotting factors, immunoglobulins have been demonstrated to be a major cause of infection with HCV. At present, these kind of preparations can be used in patients only after a routine testing for HCV and adequate procedures used to inactivate viruses - heat inactivation or pasteurization.<sup>39-43</sup>

### **Risk factors for HCV infection in dialysis patients - duration and mode of dialysis**

The interval since beginning dialysis has been reported to be significantly longer among anti-HCV-positive patients compared to anti-HCV negative patients, and the likelihood of HCV infection

increases considerably after a decade of HD. The risk of acquiring HCV infection on hemodialysis has been estimated at 10% per year.<sup>24</sup>

Numerous studies have demonstrated the clear relationship between HCV infection and the duration of dialysis (years), independently from blood transfusions.<sup>44</sup> This observation suggests that HCV infection can be acquired in patients of the same unit of dialysis, probably due to various factors: the deficiencies in adherence to “universal precautions”, poor attention to hygiene and sterilization of dialysis machines, the low socio-economic level or education of the patients (“bad habits” observed in some patients – sharing of medications, vials and other sanitary products).

Peritoneal dialysis is infrequently involved as a primary cause of HCV infection, with a risk of infection 8-9 times lower than hemodialysis. In contrast to hemodialyzed patients, the duration of peritoneal dialysis is not a risk factor for acquiring HCV infection.<sup>11</sup> Moreover, when patients on peritoneal dialysis develop anti-HCV antibodies, they usually acquired the infection while on hemodialysis. In a study published by Weinstein et al in dialysis patients, all patients with HCV infection have been also on hemodialysis.<sup>45</sup>

The following factors are responsible for the lower risk of HCV infection among peritoneal dialysis patients: these patients have a lower requirement for blood transfusion, the absence of extracorporeal blood circuit, the procedure can be performed – at least in the West – as a home procedure, conferring a more protected and secure environment.

#### **Prevalence of HCV infection in the dialysis unit**

The prevalence of HCV infection in the dialysis units is important, because of all factors mentioned above.<sup>38</sup> A study published by the Portuguese Society of Nephrology reported a direct correlation between the incidence of HCV infection and the prevalence of the HCV infection in the dialysis units.<sup>39</sup>

Other studies have documented the possibility of HCV transmission from a patient to another in the same dialysis unit, using PCR and phylogenetic analysis, identifying the same genotype and genome structure in these patients.<sup>44,46,47</sup> In addition, it seems that there is a direct correlation between the dominant HCV genotype in that geographical area and the HCV genotype demonstrated in dialysis units.<sup>48,49</sup>

Other accepted risk factors for anti-HCV positivity in dialysis patients are:

- history of organ transplantation, reflecting the infection in donor organs;<sup>50</sup>
- history of intravenous drug abuse, ranging from

30%-73% in US studies;<sup>51,52</sup>

- history of endoscopic or other invasive procedures (catheterism);<sup>53-58</sup>
- male gender.<sup>59</sup>

## **NOSOCOMIAL TRANSMISSION IN HEMODIALYSIS DEPARTMENTS**

Risk factors identified for HCV transmission to patients or healthcare persons are:

- transmission by needle-stick injury;
- poor infection control practices;
- proximity to an infected patient;
- dialysis equipment and machines, dialyzer membranes, ultrafiltrate and peritoneal fluid;
- reprocessing of dialyzers.

### **1. Transmission of infection by needle-stick injury**

The risk of transmission of HCV from infected patients to medical staff by needle stick injury ranges from 2.7-10%.<sup>58,59</sup> Despite this not unremarkable risk, the prevalence of anti-HCV among dialysis staff is comparable to that in blood donors, at least in the West. In 1995, for example, 16% of the dialysis centers in the United States tested staff members for anti-HCV; among the 6236 staff members tested, the prevalence of anti-HCV was 2.0% (range 0 to 10% in centers with at least 20 staff members).<sup>60</sup>

### **2. Breakdown in standard infection control practices**

Obviously strict adherence to standard precautions and control practices will offer a more secure environment for patients and staff in hemodialysis units.<sup>61,62</sup> From this point of view, it is absolutely necessary to accept the following measures:

- early recognition/diagnostic of patients with HCV infection;
- sharing of personal hygienic items or medication vials among patients with or without HCV infection;
- changing gloves between patients on dialysis treatment;<sup>61,62</sup>
- rigorous infection-control measures, cleaning and disinfection of all instruments and environmental surfaces that are routinely touched.<sup>61-63</sup>

### **3. Physical proximity to an infected patient**

This issue is very concerning, mainly because this observation has been emphasized in the West, where the prevalence of HCV infection in hemodialysis patients is less frequent in comparison with countries like Romania. Dialysis patients infected with HCV represent a major risk factor for other patients from the same hemodialysis unit.<sup>64</sup> A Portuguese Society

of Nephrology survey found the lowest incidence of HCV infection in HD units that used isolated rooms to treat anti-HCV positive patients.<sup>39</sup>

A very recent study, published in 2005 by a team from Spain, concerning the risk of HCV transmission in a liver tertiary unit (where the risk factors are not so clear, in contrast to dialysis units), from patients with HCV infection to other patients admitted in the same unit, found that the proximity to such patients has been the main cause of HCV transmission in 0,46% patients.<sup>65</sup>

#### 4. Dialysis machines

Many studies have linked a high incidence of HCV infection in dialysis patients who shared dialysis machines in the hemodialysis unit.<sup>66-68</sup> The use of dedicated machines and isolated areas for anti-HCV positive patients along with strict enforcement of universal precautions was associated with a decrease in the incidence of seroconversion.<sup>39,64,68-72</sup>

Furthermore, vertical transmission of HCV by dialysis machines may be possible, and only systematic monitor disinfection is an effective tool in preventing nosocomial transmission of HCV, conclusion demonstrated also experimentally.<sup>70,73</sup>

#### 5. Dialyzer membranes, hemodialysis ultrafiltrate, and peritoneal fluid

Neither theoretically (HCV viral particles have an estimated diameter of 35 nm, much higher than the pores of even the most permeable dialysis membrane), nor practically, the passage of HCV through intact dialyzer membranes seems impossible, no matter what kind of dialyzer are used - low-flux (cellulose) or high-flux (cellulose-diacetate, polysulfone and polyacrylonitrile).<sup>74,75</sup> Nevertheless, Lombardi M et al in 1995 have demonstrated HCV-RNA by PCR in the dialysate of apparently intact polyacrylonitrile membranes, but not cellulose membranes.<sup>74</sup> It is important to emphasize that detection of HCV RNA in the dialysate by PCR may only imply the presence of small fragments of viral RNA, a situation which may not lead to transmission of the infection.

HCV has been found in several organic fluids including ascites. Since most studies suggest that HCV-RNA is present in the peritoneal dialysis effluent of some patients, the effluent should be considered infectious material.<sup>76</sup>

#### 6. Reprocessing of dialyzers

Reprocessing of dialyzers does not seem to enhance the risk of HCV transmission.<sup>39,70,77</sup> However, Dos Santos and colleagues have demonstrated a lower incidence in patients in units that used separate rooms to reprocess dialyzers from anti-HCV positive and

anti-HCV negative patients.<sup>39</sup>

All these studies suggests that dialyzer reprocessing does not have a significant contribution to the nosocomial transmission of HCV.<sup>77</sup>

## CONCLUSIONS

In conclusion, the HCV infection incidence and prevalence in HD units remains very important, especially in Romania. The ELISA 3 anti-HCV test and transaminases must be determined at least every 6 months, but only very rigorous infection control measures can and will prevent further nosocomial HCV transmission among HD patients.

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