HEPATITIS C IN DIALYSIS PATIENTS

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A b s t r a c t: Hepatitis C virus (HCV) remains prevalent in dialysis patients and is an important cause of liver disease in this population. A number of risk factors have been identified for spreading the HCV infection among dialysis patients, including the number of blood transfusions, the duration of dialysis, the mode of dialysis, and the prevalence of HCV infection in the dialysis unit. Difficulties in formulating policies regarding HCV infection in dialysis units arise because of the high prevalence of HCV infection in dialysis patients, the limitations of current tests in identifying these patients, and the uncertainties regarding the modes of transmission within dialysis unit.

Little is known concerning the natural history of HCV infection in patients undergoing dialysis. This is due in part to an unrecognized onset of infection, the slow progresssion of hepatitis C viral disease, and the fact that infected dialysis patients may not have the time to become clinically apparent because of the overall shortened life-expectancy. The clinical course of HCV infection in dialysis patients is generally asymptomatic, and the progression of the disease is apparently benign. The mortality rate of infected dialysis patients is higher than in non-infected subjects, and this is not only due to the liver disease itself but also to cardiovascular disorders.

Interferon α (standard or pegylated) is the current treatment of HCV infection in dialysis patients, with careful patient selection together with a close follow-up of the main side effect. HCV infected dialysis patients who are candidates for renal transplanttation have to be treated before transplantation, since HCV infection has a negative impact on graft and patient survival and interferon therapy remains contraindicated after transplantation because of the serious risk of graft rejection.

Key words: Hepatitis C virus infection, dialysis, epidemiology, diagnosis, prevention, therapy.

Introduction

Hepatitis C virus (HCV) infection in dialysis patients represents a significant health problem for dialysis units, both in term of containing the spread of infection, and following the clinical progression of infected patients. Dialysis patients are a group at particularly high risk of acquiring HCV infection because of nosocomial spread. The natural history of HCV in dialysis patients remains controversial because the course of HCV typically extends over decades, while dialysis patients have higher morbidity and mortality rates than those reported in the general population limiting long-term follow-up. Liver disease due to HCV infection is a significant cause of morbidity and mortality in end-stage renal disease patients treated with dialysis or transplantation. Anti-viral therapy, after its first timed steps, is now routinely used in dialysis patients with a certain degree of liver damage and kidney transplant candidates [1, 2].

Structure of the HCV genome

In 1989 the HCV was cloned and identified as the major cause of parenterally transmitted non-A, non-B hepatits (NANBH). HCV is a flavivirus composed of a 10 kb single positive strand RNA. The viral genome encodes a precursor polyprotein of about 3000 amino acids, co- and post-transcriptional cleavages of which generate the core, seven non-structural (p7, NS2-5) proteins and two glycoproteins which constitute the envelope proteins E1 and E2 [3, 4]. Several HCV genotypes have been identified and significant genetic heterogeneity has been observed over the entire viral genome. The regions encoding the E1 and E2 are the most variable sequences of the viral genome, while the 5' non-coding region (5'NCR) represents the most conserved one (Figure 1).
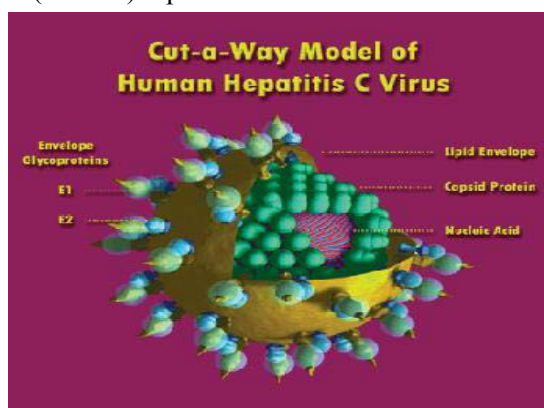

Figure 1 – Cut-a-way model of HCV with the presentation of lipid envelope,
envelope glycoprotein (E1 and E2) and nucleotides.
Слика 1. – Модел на HCV со презентација на липидната обвивка,
гликопротеините во обвивката (E1 и E2) и нуклеотидите

The universal system for the nomenclature of HCV genotypes has defined six major genotypes (1 to 6), designated as HCV types [5]. Each major type consists of one or closely related variants, designated as subtypes and named a, b, etc. in order of discovery. Finally, each subtype includes individual isolates.

Tests for HCV RNA

The detection of HCV RNA by reverse transcriptase polymerase chain reaction (RT-PCR) has been used as the "gold standard" to identify current HCV infection [6]. In patients with post transfusion NANBH due to HCV, high levels of HCV RNA in the circulation can be detected by PCR within one week of exposure and prior to the appearance of anti-HCV or elevation in ALT levels [7, 8]. There are two types of PCR assays presently available: *qualitative and quantitative.*

The qualitative polymerase chain reaction (PCR) assays report results as the presence or absence of HCV RNA in the serum. These assays are considered the most sensitive tests for diagnosis of HCV infection. The reliability of these tests might be limited by false positive or negative results. Imperfect handling and/or storage of blood samples can lead to failure to detect HCV RNA in up to 40% of samples [9]. Whole blood anticoagulated with EDTA or with mixed anticoagulants may be stored at up to 25 degrees C (room temperature) for up to five days without any significant loss in plasma HCV RNA level [10] and the measures are required to prevent false positive results from even minor contamination [11, 12].

Quantities of HCV RNA titers, i.e. defining the number of HCV RNA copies per millilitre of serum, can be done with the use of quantitative reverse transcriptase PCR (RT-PCR) assays or branched chain DNA (bDNA) assays [11]. Significant short-comings of the quantitative RT-PCR assays are their labour-intensive performance, lack of standardization, and wide variations in sensitivity and specificity. By comparison, the bDNA assays are automated, simpler to perform, and more reproducible, though less sensitive than quantitative RT-PCR tests.

In clinical practice, quantitative tests for HCV RNA should not serve as an initial diagnostic tool for HCV infection, but should be reserved for pre-treatment evaluation and monitoring patient response to antiviral treatments. Because of the great variability in sensitivity and lack of standardization across the assays and laboratories, when a patient is tested repeatedly for antiviral therapy, it is critical to use the same test and the same laboratory where previous testing was preformed [12].

The most commonly used system for classification and nomenclature of HCV genotypes is based upon the nucleotide sequence comparison of the NS5

region [5]. Although numerous tests can be used for HCV genotyping, the nucleide acid sequencing of the NS5 region is generally considered to be the gold standard. HCV genotyping is mostly used as a tool for research or epidemiological investigation tracing the source of infection. HCV genotype testing is unnecessary for the diagnosis of the HCV infection, but may eventually be useful in clinical practice to assist in tailoring antiviral therapy to the individual patient's HCV genotype.

Tests for HCV antibodies

Tests for antibodies to HCV (anti-HCV) are the mainstay of the clinical diagnosis of HCV infection. Enzyme-linked immunosorbent assays (ELISA) and recombinant immunoblot assays (RIBA) have been used to detect non-neutralizing antibodies. ELISA detects an antibody to a specific HCV antigen (first generation tests) or to a combination of antigens (second and third generation tests) in a standard ELISA plate. In contrast, the RIBA detects antibodies to one or more HCV antigens on a strip that is read visually.

While ELISA have been used as screening tests [13], RIBA have been considered confirmatory tests by virtue of their increased specifity. The second generation test can detect seroconversion as early as four weeks after exposure [14]. The third generation anti-HCV tests, which are currently largely in use, have shown a better performance than the previous two generations of anti-HCV test [15]. In addition, the window period has been further reduced and is estimated at a mean of 70 days [16].

Tests for HCV core antigen

Tests have been developed to detect the presence of viral antigenemia using a monoclonal antibody to the HCV core antigen (HCVc Ag) [17]. A commercial ELISA test for "free" HCVc Ag is available in some countries. Other tests that detect "total" HCVc Ag, both free and complexed with anti-HCV antibody, are presently undergoing evaluation [24]. Preliminary results indicate that assays for HCVc Ag have excellent correlation with virologic tests for HCV RNA and make it possible to detect HCV infection prior to anti-HCV seroconversion, confirm anti-HCV positive status, assess patient infectivity, depict those anti-HCV patients who are most likely to be viremic, and monitor the dynamics of the infection as well as the thera-peutic response in individuals receiving antiviral treatments [24]. These tests seem to be a viable alternative to HCV RNA testing and are likely to find a large clinical application.

Difficulties in interpreting HCV tests

Two combinations of anti-HCV and HCV RNA results among patients exposed to HCV can produce difficulties in the interpretation of test results:
– the anti-HCV positive and HCV RNA negative patient, and
– the anti-HCV negative and HCV RNA positive patient.

The anti-HCV positive and HCV RNA negative patient

The anti-HCV tests that are currently licensed for clinical use detect non-neutralizing antibodies to recombinant HCV antigens. As a result, the presence of anti-HCV does not necessarily imply the presence of HCV RNA in the serum. As an example, HCV RNA has been detected in only 52% to 93% of dialysis patients who are anti-HCV positive. However, preliminary evidence suggests that the presence of IgM anti-HCV may serve as a complementary marker of virus replication [25]. Several possibilities could account for the presence of anti-HCV in the absence of HCV RNA [19, 20]:

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

– Viremia could be intermittent. HCV RNA may therefore not be present in the plasma at the time of testing. In one study, 35% of anti-HCV positive dialysis patients demonstrated a fluctuating pattern of viremia with virus-free intervals [21].

– The number of copies of HCV RNA may be below the limit of detection.

– Antibody to HCV may persist even after the viral RNA has disappeared, representing patients who had been infected with the virus, but no longer harbour it.

– Anti-HCV may have been passively acquired from blood transfusions. In this situation, anti-HCV would disappear over the following weeks in keeping with the half-life of IgG.

– 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 anti-HCV negative and HCV RNA positive patient

Although more than 90% of immunosuppressed individuals with HCV infections test positive for anti-HCV, some patients are anti-HCV negative despite being positive for HCV RNA. Possible explanations for these results include:

– The anti-HCV test may not be sensitive enough to detect an existing anti-HCV antibody. This may result from either a low titer of antibody or because the antigen used in the assay system cannot detect the serum antibody response to the particular genotype.

– Various diseases, conditions or pharmacological immunosuppression could suppress or modify the anti-HCV response [23].

– The patient may be in the "window" period between infection and anti-HCV seroconversion.

– After an 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 from haemodialysis patients without anti-HCV or HCV RNA in the serum. The HCV RNA in these cells could therefore serve as a viral reservoir to identify HCV infection.

Clinical course of HCV infection

Acute HCV infection is often mild and associated with few, if any symptoms. Fulminate or severe cases are rare. The major complication of acute HCV infection is chronic infection, which occurs in up to 70% of cases. Neither clinical, laboratory nor serological features of acute infection predict whether infection will resolve or persist [23]. During the acute infection, HCV RNA levels fluctuate, and some patients are intermittently negative according to current assays despite ultimately developing chronic disease with high viral levels [25]. At present, the continued presence of HCV RNA for 6 months after (estimated) onset defines chronic infections, and subsequent spontaneous loss of virus is unusual [26].

The natural history of chronic HCV infection has been the subject of many studies but remains only partially defined [23]. The initial onset of acute infection is often not recognized. Evolution from acute to chronic hepatitis ensues without clinical signs, and chronic hepatitis continues for decades before clinically apparent end-stage liver disease emerges, if it does at all [25]. The major long-term complication of chronic hepatitis C is hepatic fibrosis, which can eventuate in cirrhosis, portal hypertension, and hepatic failure. Patients with cirrhosis are also at high risk of hepatocellular carcinoma (HCC). The development of cirrhosis in published studies has ranged from 2% to 42% [26]. Combined data suggest that the progression of the disease is uncommon and slow in children and young adults, but more rapid in older individuals (Figure 2).
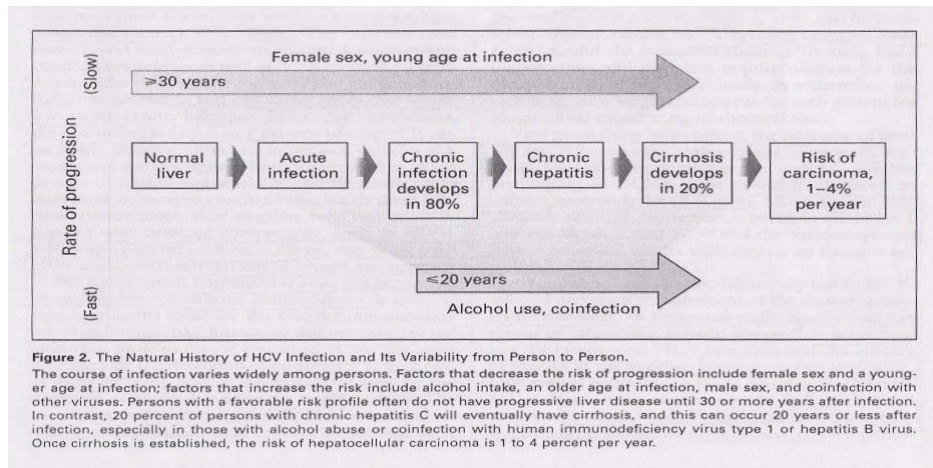
Figure 2. The Natural History of HCV Infection and Its Variability from Person to Person.
The course of infection varies widely among persons. Factors that decrease the risk of progression include female sex and a younger age at infection; factors that increase the risk include alcohol intake, an older age at infection, male sex, and coinfection with other viruses. Persons with a favorable risk profile often do not have progressive liver disease until 30 or more years after infection. In contrast, 20 percent of persons with chronic hepatitis C will eventually have cirrhosis, and this can occur 20 years or less after infection, especially in those with alcohol abuse or coinfection with human immunodeficiency virus type 1 or hepatitis B virus. Once cirrhosis is established, the risk of hepatocellular carcinoma is 1 to 4 percent per year.

Figure 2. The natural history of HCV infection and its variability from person to person (Lauer, NEJM 2001)

Слика 2. Природен ȳек на HCV инфекцијаȳа и нејзинаȳа варијабилносȳ кај различни индивидуи (Lauer, NEJM 2001)

Several factors correlate with a greater rate of progression of liver fibrosis [23]. Viral factors, such as HCV RNA level, viral genotype or quasispecies diversity, do not appear to be important. Conversely, several host factors are important, including older age, older age at onset of infection, male sex, white race, confection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), and other co-morbid conditions, such as haemochromatosis, nonalcoholic steatohepatitis, obesity, and diabetes. Among enviromental factors, chronic alcoholism undoubtedly contributes to the progression of liver disease, but the lowest level of alcohol intake that accelerates progression has not been defined [23].

Natural history of HCV infection in dialysis patients

Assessing the natural history of HCV infection in dialysis patients is problematic because of the unique characteristics of this population. First, ALT levels are frequently normal and appear to be less reflective of the activity of the liver disease in HCV-positive dialysis patients compared with patients without renal disease [27]. Second, anti-HCV testing may not be reliable in dialysis patients because of the blunted humoral immune responses that occur with renal disease. A small proportion of patients with end-stage renal disease (ESRD) have HCV RNA in the serum, but lack detectable anti-HCV [28]. Third, liver biopsy is the typical gold standard for assessing the severity of hepatitis C, but has yet to be applied to a large number of dialysis patients. Finally, chronic hepatitis C has an insidious and prolonged natural history and the competing

mortality of complications of ESRD and haemodialysis may obscure the long–term consequences of hepatitis C [29].

Cross-sectional studies have provided an overview on the spectrum of liver disease in HCV-positive dialysis patients [30, 31, 32]. Disease activity was reported to be mild to moderate in most series, and a high proportion of patients had normal ALT levels. Among patients with post-transfusion hepatitis C, HCV RNA was detected in the serum one or three weeks after exposure, followed several weeks later by elevated serum ALT levels. Among such patients, 50% had self-limited disease and 50% had persistently elevated serum ALT levels [7]. Importantly, the proportion of patients with advanced fibrosis or cirrhosis tended to be low. In these studies, the frequency of bridging hepatis fibrosis (stage 3) or cirrhosis (stage 4) ranged from 5% to 32%. In most studies, there were no associations between ALT or HCV RNA levels and the severity of histological changes, indicating that liver biopsy is the only accurate means of assessing hepatitis C disease severity.

Little is known concerning the natural history of acute and chronic HCV infection in patients undergoing maintenance dialysis [33]. This is due in part to the unrecognized onset of infection and the slow progression of hepatitis C viral disease, and infected patients may not have the time to become clinically apparent because of their overall shortened life-expectancy. A prospective study of 19 dialysis patients with acute infection found that, at a median follow-up of three years, nearly 80% remained viremic [34]. Overall, approximately 60% had increased ALT levels and positive HCV RNA, with five patients exhibiting chronic active hepatitis on liver biopsy. Four patients (21%) cleaned the viral infection.

The time required to develop liver complications from HCV can be prolonged. In a study from Seattle, WA, 220 patients, of whom 34 patients were HCV RNA positive, were followed up for an average of 3 years [35]. Multivariate analysis showed an increased relative risk (RR) of death in HCV RNA-positive patients of 1.78 (95% CI, 1.01 to 3.14). In a multicentre prospective study from Japan, 1470 patients (19% positive for anti HCV) from 16 dialysis centres were followed up for an average of 6 years [36]. Mortality was greater in the anti-HCV-positive group (33%) than in controls (23%), and the excess mortality appeared to be accounted for by death from cirrhosis (5.5% vs. 0%), and HCC (8.8% vs. 0.4%). The RR for death in anti-HCV-positive patients was 1.57 (95% CI, 1.23 to 2.0). In a study from the USA, 287 anti-HCV-positive and 286 randomly selected dialysis control patients from 14 transplant centres were assessed, with a median follow-up of 7 years [37]. In a multivariate analysis RR for death from all causes in ant- HCV-positive was 1.41 (95% CI, 1.01 to 1.97), and for death from liver disease or infection was 2.39 (95% CI, 1.28 to 4.48). Death from liver disease occurred in 14% of anti-HCV-positive and only 2% of anti-HCV-negative controls. These data show that chronic hepatitis C adversely affects survival in patients with ESRD, cirrhosis and liver cancer account for 13% to 14% of deaths.

Relationship among serum ALT, HCV infection, and liver disease

In general, elevation in serum levels of ALT is associated with the probability of histological evidence of the liver disease in the HCV infection. This correlation however is weak. In addition, serum ALT levels are poor predictors of liver disease. Among dialysis patients, for example, serum ALT levels are elevated in 4 to 67% of anti-HCV-positive patients, 12 to 31% of patents with HCV RNA and one-third of patients with biopsy-proven hepatitis (19,38). Similarly, biochemical evidence of liver HCV RNA disease is present in only 42 to 52% of HCV RNA-positive renal transplant recipients [39].

The discrepancy between serum ALT levels and presence of anti-HCV is due to the following reasons:

– chronic HCV infection characteristically has a fluctuating course with multiple peaks and troughs in ALT levels. Thus, patients with normal ALT levels may have severe histological lesions.

– HCV infection is not always associated with chronic liver disease. In one report, only 69% of anti-HCV-positive symptom-free blood donors who underwent liver biopsy had histological evidence of chronic hepatitis.

– As discussed earlier, some anti-HCV-positive patients may have cleared the infections and anti-HCV may be the reminder of past infection.

– Baseline serum ALT levels are depressed in patients on dialysis [40].

However, elevated serum ALT has been observed in 4 to 23% of anti-HCV-negative dialysis patients [19, 38]. These patients could be carriers of HCV infection in whom anti-HCV production is absent, or the liver disease might be due to an NANB virus other than HCV or non-viral causes.

Liver biopsy

Liver biopsy remains the only reliable method of confirming the presence and assessing the severity of liver disease in patients with HCV infections. Liver histology at the time of initial presentation has been shown to be a good predictor of the intermediate and long-term outcome in renal transplant recipients with liver disease [41]. Over a mean follow-up of 6 years, progression to liver failure and death was rare in transplant recipients with mild histological abnormalities such as fat metamorphosis or chronic persistent hepatitis [41]. In contrast, 35% of recipients with early chronic active hepatitis and 60% with advanced chronic active hepatitis progressed to liver failure and death. At present, it is necessary to perform a liver biopsy in dialysis patients in whom serum ALT levels are persistently elevated [26]. Patients with normal serum ALT levels are biopsied only if they are being considered for transplantation.

Epidemiology of HCV infection

The HCV infection continues to be a major disease burden on the world. Incidence rates across the world fluctuate and are difficult to calculate, due to the asymptomatic, often latent nature of the disease prior to clinical presentation. Prevalence rates across the world have changed. More countries are aware of transfusion-related hepatitis C but more evidence supports intravenous drug use as the leading risk factor in the spread of the virus [42].

In 1999, the WHO estimated a worlwide prevalence of about 3% with the virus affecting 170 million people worldwide [43] (Table 1).

Table 1 – Табела 1

Hepatitis C estimated global prevalence and number infected by WHO region
Глобална превеленција на HCV инфекцијата
според Светска здраствена оранизација

WHO region	Total population (Millions)	Hepatitis C prevalence rate (%)	Infected population (Millions)	No data available (Number of countries)
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7
Eastern Mediterranean	466	4.6	21.3	5
Europe	858	1.03	8.9	19
South-East Asia	1500	2.15	32.3	3
Western Pacific	1600	3.9	62.2	11
Total	5711	18.7	169.7	57

The HCV infection has became the main indication for liver transplantation in the USA [44]. The current mortality figures are projected to increase 2- to 3-fold over the next 1 to 2 decades as patients with HCV infection develop cirrhosis and end-stage liver disease. Using the past incidence of HCV infection, it has been projected that the number of persons infected could increase substantially for more than 20 years before peaking in 2015 [45].

The prevalence of anti-HCV antibodies among patients on dialysis is consistently higher than in healthy populations, suggesting that dialysis patients may be at higher risk of acquiring HCV infection. The reported incidence, however, varies based in part upon the type of laboratory assay used. Using ELISA from the first generation (ELISA I), for example, the prevalence of HCV antibodies among dialysis patients has been reported to range from: 8 to 36% in North America, 39% in South America, 1 to 54% in Europe, 17 to 51% in Asia,

1.2 to 10% in New Zealand and Australia [19,38]. The advent of ELISA from second generation (ELISA II) revealed an even higher prevalence of HCV antibodies among dialysis patients. Pooled data from studies in which dialysis patients were tested by both ELISA I and ELISA II revealed that ELISA II identified more that twice the number of patients with HCV antibodies than ELISA I [38]. Using second generation HCV antibodies tests, the prevalence of anti-HCV among dialysis patients has been reported to be: 25 to 36% in USA, 2 to 63% in Europe and 22 to 55.5% in Asia [19,38]. Third generation anti-HCV tests (ELISA III) are currently largely in use. Compared to ELISA II, they have shown greater sensitivity and specificity in patients receiving renal replacement therapy [46-48]. Using such a test, the prevalence of HCV antibodies among dialysis patients was found to be 5.5 to 10% in the USA [48], 13.5 to 31% in Italy [47, 49], 42% in France [50], 75% in Moldavia [51]. Recently, Fabrizi *et al*. reported the prevalence of HCV infection in the general and the dialysis population world-wide [52, 52A] (Table 2).

Table 2 – Табела 2
Prevalence of HCV infection in general and dialysis population
Преваленција на HCV инфекцијата во ѓенералната и дијализната
population

Country	Prevalence in general population	Prevalence in dialysis population	reference (year)
Netherlands	0.1%	3%	1998
Italy	0.5%	22.5%	1999
Belgium	0.9%	9.4%	1998
Bulgaria	1.1%	65.8%	1998
France	1.1%	16.3%	2000
Turkey	1.5%	31.4%	1998
USA	1.8%	10%	2003
Saudi Arabia	1.8%	57%	2001
Moldavia	4.9%	75%	1999
Egypt	18.1%	80%	2000

Prevalence of HCV infection among the dialysis population in the Republic of Macedonia is also very high and is a serious problem. We examined 200 sera from patients on maintenance haemodialysis in 2003 [54]. The following markers were determined: anti-HCV antibodies, HBsAg, anti-HBs antibodies, anti-HBc antibodies, HIV-1 and HIV-2 antigens and antibodies. The methods used for determination were Enzyme-Linked Immunosorbent Assay (ELISA III)

and Enzyme-Linked Fluorescent Assay (ELFA). The methods used for determination of HCV were the commercially available Amplicor test kit (Roche Diagnostics), and the in-house developed RT/PCR method. Analysis of the HCV genotypes was performed by dot blot hybridization. Serum levels of alanine aminotrasferase (ALT), aspartate aminotranferase (AST) and bilirubin were also determined in each patient. Of the examined 200 sera, 109 (54.5%) were positive for anti-HCV antibodies; 19 (9.5%) were positive for HBsAg; 86 (43%) were positive for anti-HBs antibodies and 114 (57%) were positive for anti-HBc antibodies. Only 34 sera (17%) were negative for the investigated markers of HBV and HCV infection. HCV and HBV co-infection was found in 9 patients. All 200 sera were negative for HIV-1 and HIV-2, both for antigens and antibodies. The results indicated a high prevalence of HCV infection among patients on haemodialysis, 96.6% being of genotype 1 and 3.4% of undetermined genotype. The prevalence of HBV infection was also significant. Over the past 30 years, we have not had a single positive patient for HIV infection in the dialysis unit. The HCV infection correlated positively with the number of blood transfusions given to the patients, and with the period of time spent on maintenance haemodialysis. The nosocomial type of transmission was probably the dominant means of HCV spread in the dialysis unit. We would advocate strict enforcement of the universal measures for infection control, and assignment of patients to different dialysis machines, depending on their viral marker positivity [53–55].

The incidence and prevalence of HCV infection among dialysis patients is steadily declining. The decline was initially due to the reduction in post-transfusion HCV infections, subsequently, it has reflected the implementation of infection-control measures to prevent nosocomial transmission within dialysis units [56]. Nonetheless, the 0.4 to 15% incidence of anti-HCV in dialysis units continues to be a cause for concern [38]. Incidence *de novo* of HCV infection in dialysis units has been described by Li Vecchili M *et al*. (Table 3) [1].

Table 3 – Табела 3

Incidence de novo of HCV infection in dialysis units
Инциденција de novo на HCV инфекцијата во центрите за дијализа

	No of units	No of patients	Years	Incidence %
France	**25**	**1323**	**1997–2000**	**0,4**
Italy	**1**	**72**	**2000–2003**	**1,38**
Netherlands	**9**	**450**	**1995–1997**	**0,5**
Spain	**7**	**890**	**1992–2002**	**0,5**
Tunisia	**10**	**395**	**2001–2003**	**0,5**
Japan	**9**	**2744**	**1999–2003**	**0,33**

Risk factors for HCV infection in dialysis patients

A number of risk factors have been identified for HCV infection among dialysis patients, including the number of blood transfusions, the duration of ESRD, the mode of dialysis, and the prevalence of HCV infection in the dialysis unit.

Number of blood transfusions

In numerous studies, anti-HCV-positive dialysis patients had received significantly more units of blood products than anti-HCV-negative patients [58]. Fortunately, since the introduction of erythropoietin and screening of blood products for anti-HCV, the risk of acquiring post-transfusion HCV infection has declined to less than 1 per 3000 units of blood products transfused [59].

Duration 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 dialysis treatment [58].

Mode of dialysis

Patients on peritoneal dialysis (PD) are at lower risk of HCV infection and, in contrast to haemodialyzed patients, the duration of PD does not appear to be a risk factor for acquiring HCV infection [38]. In addition, the majority of anti HCV positive PD patients may have acquired HCV infection while they have been on hemodialysis. One or more of the following factors can account for the lower risk of HCV infection among PD patients:

– PD patients have a lower requirement for blood transfusion than haemodialysis patients

– The absence of access site and extracorporeal blood circuit reduces the risk of parenteral exposure to the virus

– PD offers a more isolated environment since it is a primarily home procedure.

Prevalence of HCV infection in the dialysis unit

Patients treated in dialysis units with high prevalence of HCV infection are at increased risk of acquiring infection. A survey by the Portuguese Society of Nephrology, for example, found that the incidence of HCV correlated directly with the prevalence of the HCV infection in the dialysis unit. Among

units with a prevalence of less then 19%, the annual incidence of seroconversion for anti-HCV was 2.5%. By comparison, among units with a prevalence of HCV infection greater than 60%, the annual incidence of seroconversion was 35.3% (60–63).

Other factors

There are other risk factors for acquring the HCV infection in the dialysis unit:

– A history of previous organ transplantation (maybe transmission from the organ donor)

– Intravenous drug abuse

– Male gender: in addition, one study found that male dialysis patients infected with HCV had a significantly higher concentration of serum HCV RNA than females (64,65).

Nosocomial transmission of HCV infection in dialysis unit

Several of the following factors may affect the risk of transmission of HCV to patients and staff in dialysis units:

– Transmission of HCV from infected patient to dialysis staff by needle-stick injury

– Breakdown in standard infection control practices

– Physical proximity to an infected patient

– Dialysis machines

– Dialyzer membranes, haemodialysis ultrafiltrate, and peritoneal fluid

– Reprocessing of dialyzers.

Transmission of HCV from infected patient to dialysis staff by needle-stick injury

The risk of transmission of HCV from infected patients to medical staff by needle-stick injury ranges from 2.7 to 10%. Despite this risk, the prevalence of anti HCV among dialysis staff is comparable to that in blood donors [64, 66].

Breakdown in standard infection control practices

Several outbreaks of HCV infection in dialysis units have been associated with a failure to rigidly enforce universal precautions and standard infection-control measures, such as sharing of a multi-dose heparin vial between patients with and without HCV infection and failure to change gloves between patients while performing dialysis treatments [67–69]. HCV RNA has also been

detected on the hands of some dialysis staff despite apparent adherence to standard precautions [70]. This observation raises the possibility that dialysis staff could be a potential vector for HCV transmission between dialysis patients.

Indirect evidence suggesting that infection results from breaks in infection-control practices was provided by an Italian study of 58 dialysis units [71]. An increased risk of HCV infection was associated with being dialyzed in a centre unit with a high prevalence of HCV-infected patients and a low personnel to patient ratio.

Rigorous infection-control measures, cleaning and disinfection of all instrument and environmental surfaces that are routinely touched and a ban on sharing of articles among patients, results in a decline in the incidence of HCV infection. A multicentre prospective study from Belgium unequivocally demonstrated that enforcement of universal precautions alone could fully prevent transmission of HCV in dialysis units [61].

Physical proximity to infected patients

In a multicentre study in Belgium, 38% of the dialysis patients who seroconverted had never been transfused and had no apparent risk factor for HCV infection [61]. Clustering of seroconversion occurred only in dialysis units in which anti-HCV-positive patients were being treated [61]. A Portuguese Society of Nephrology survey found the lowest incidence of HCV infection in dialysis units that used isolated rooms to treat anti-HCV-positive patients [60].

Dialysis machines

Several reports have linked a high incidence of HCV infection in dialysis patients who shared dialysis machines in dialysis unit [72–74]. In addition, 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 [75, 76]. Similarly, a survey by the Portuguese Society of Nephrology found a significantly lower incidence of HCV infection in units that used dedicated machines for anti-HCV-positive patients [60].

However, the need for isolation and the use of dedicated machines for anti-HCV-positive patients has been challenged. In a multicentre study from Belgium, for example, no new cases of HCV infected patients occurred over a 54-month study period, despite the observation that none of the participating dialysis centres used dedicated machines for anti-HCV-positive patients, and over 70% of the patients were dialyzed in units whose monitors were not disinfected after each session [61]. Another study also questioned the benefit of using dedicated machines but provided evidence favouring the practice of separating anti-HCV-positive patients. The rate of nosocomial transmission of HCV was higher in a dialysis unit in which both anti-HCV-positive and anti-HCV-negative pa-

tients were treated together than in another unit where dialysis treatment was provided only for anti HCV negative patients [77].

Systematic monitor disinfection, use of dedicated machines, and strict adherence to universal precautions are an effective tool in preventing nosocomial transmission of HCV in dialysis units [78,79].

Dialyze membranes, haemodialysis ultrafiltrate, and peritoneal fluid

Theoretically, the passage of HCV through intact dialyze membranes seems improbable as the viral particles have an estimated diameter of 35 nm, much higher than the pores of the most permeable dialysis membrane. Nevertheless, the passage of the virus into the dialysis compartment could result from any alteration in pore size or disruption of the membrane integrity associated with the process of filter assembly, the dialysis session itself, or with dialyzer reuse.

Two studies have reported that neither low-flux nor high-flux dialyzers permit contamination of the dialysis ultra filtrate with HCV RNA [80, 81]. In similar reports, other investigators suggest that lower transmembrane pressure should be used in anti HCV positive patients to minimize the risk of HCV transmission [82]. In contrast, others have detected HCV RNA by the PCR method in the dialysate of apparently intact polyacrylonitrile membranes but not in cellulose membranes [83].

To elucidate whether the HCV may pass across the membrane, we have performed an analysis of ultra filtrates collected at different stages of dialysis treatment, using different types of dialysis membranes. HCV was found in 17 out of 58 ultra filtrates samples taken at different times of the dialysis treatment of HCV-infected patients. Moreover, HCV RNA was present in 15 out of 17 samples collected from the dialyze compartment during the saline solution rising step of the blood compartment of HCV RNA positive patients. There was no association between the presence of HCV in the ultra filtrates and the type of dialysis membrane [84]. It is important to emphasize that detection of HCV RNA in the dialysate by PCR may only imply the presence of fragments of viral RNA, not the infective virus itself, a situation which may not lead to transmission of the infection.

Many studies suggested that HCV RNA was present in the PD effluent of some HCV-infected patients, and the effluent should be considered infectious material [85, 86].

Reprocessing the dialyzers

In a prospective study of 15 dialysis units in Belgium, the incidence of HCV infection in patients treated in units that reprocessed dialyzers was comparable to those that did not [61]. However, among units that did reprocessing of the dialysers, the lowest incidence of HCV infection was observed in patients in

units that used separate rooms to reprocess dialysers from anti-HCV positive patients. In another study, a decline in the prevalence of HCV infection in dialysis patients occurred in the presence of routine reuse of dialyzers [85]. This observation suggests that dialyzer reprocessing could not make a significant contribution to the nosocomial transmission of HCV.

Strategies to control the transmission of HCV infection in dialysis units

Difficulties in formulating policies regarding HCV infection in dialysis units arise because of the high prevalence of HCV infection among dialysis patients, the limitations of current tests in identifying these patients, and uncertainties regarding the modes of transmission within the dialysis unit. Transmission of HCV depends on the presence of chronically infected patients and potentional exposure to blood products, and recommendations are similarly based on dialysis-specific infection-control practices. In addition to standard universal precautions, further practices are recommended because exposure to blood is routinely anticipated [87, 88]. These recommendations include special dialysis unit precautions, regular serological testing, active surveillance, and education. The Centre for Disease Control and Prevention (CDC) has not recommended isolation of HCV-infected patients in dialysis units [76, 88]. But in units with a high prevalence of HCV infection, isolation of anti-HCV positive patients to dedicated machines is our suggestion. All dialysis patients should be tested for HCV antibodies on admission. For anti-HCV-negative patients, recommended monitoring includes testing serum ALT levels monthly and HCV antibodies every 6 months. Elevation in serum ALT levels should lead to HCV antibody testing. If serum ALT levels are persistently abnormal, despite the absence of HCV antibodies, testing for HCV RNA should be considered [87].

Treatment of HCV infection in dialysis patients

The recommended therapy for most patients with chronic HCV infection who do not have renal disease consists of interferon alpha (preferably pegylated interferon alpha) in combination with ribavirine. Ribavirine is cleared by the kidneys and the use of ribavirine in patients with a creatinie clearance below 50 ml/min is impaired [89].

Interferon alpha in dialysis patients with HCV infection

The role of interferon alpha (IFN α) monotherapy in dialysis patients is still evolving. A majority of treated patients have shown a decrease in serum ALT levels and an improvement in liver histology [90, 91]. At least two meta-

analyses that have been performed showed that IFN α therapy alone is associated with sustained viral response (SVR) [92, 93]. In a meta analysis of 14 clinical trials, approximately 1/3 of treated patients had SVR. In five of the trials, a standard regimen of cutaneous interferon administration (3 million units thrice weekly) given for 24 weeks was associated with SVR in nearly 40% of the treated patients. These meta analyses demonstrated that IFN α therapy in dialysis patients resulted in good biochemical and viral response, and appeared to exert a beneficial effect on the course of liver disease following renal transplantation. The efficacy and adverse effects of IFN α (3 × 3 MU/wk) administered for a period of one year were assessed in 17 dialysis patients with biopsy-proven HCV-associated chronic hepatitis [94]. A sustained viral response was observed in 71% of the treated patients. After six months of treatment, 11 of 13 patients (85%) who underwent liver biopsy showed histological improvement. Severe side-effects (lethargy and mialgia) prompted the discontinuation of treatment in only one patient. Two patients who had received a cadaver renal transplant, one year after IFN α treatment demonstrated a sustained biochemical and viral response at follow-ups at 17 and 28 months. However, as in the cases without renal failure, relapses are common after stopping the therapy and long-term outcomes are not yet adequately defined [90]. Furthermore, although the disappearance of HCV RNA from the serum is common, the currency of viremia from extravascular sites remains a distinct possibility [95].

Predictors of response to IFN α therapy

The factors that appear to underline the response to IFN α therapy include the dose and duration of therapy, pretreatment viral load, and liver histology. Higher doses of IFN α and longer duration seem to be associated with higher response rates in dialysis patients, although such regimens may result in more adverse effects [96–98]. A low pre-treatment viral load has been correlated with a SVR to IFN α therapy, whereas relatively high HCV RNA levels have been associated with a no response to IFN α therapy [99]. The value of the HCV genotype as a predictor of response to IFN α therapy is debatable. According to liver histology, the presence of liver cirrhosis on the pretreatment liver biopsy specimen was associated with a lower response to IFN α therapy in the general population with HCV infection [100]. Similarly, in dialysis patients, mild liver pathology has been found to be a predictor of SVR. Patients with decompensate cirrhosis should not be considered for IFN α therapy [99, 101].

Overview of side-effects of IFN α therapy

Treatment with IFN α is associated with side-effects and the incidence of these complications is partially related to the dose administered [102]. The largest prospective study of the tolerance and efficacy of IFN α in dialysis

patients with HCV infection was terminated after only 37 patients had been enrolled (with 120 initially requiring) because of severe adverse side-effects requiring treatment discontinuation in 19 (51%) patients [103]. Side-effects include severe asthenia, cardiac and digestive problems, and neuropsychiatric disorders. The dose of IFN α was 3 × 3 MU/wk, with a reduction to 3 × 1.5 MU/wk because of side-effects. In a meta analysis of 14 trials of IFN α therapy in 269 dialysis patients with HCV infection, the most frequent side effects were flu-like sy (17%), neurological (21%) and gastrointestinal disorders (18%) [92].

Pegylated interferon α in dialysis patients with HCV infection

A modified form of IFN α, pegylated IFN α (PEG IFN α), was developed by attaching a polyethylene glycol molecule to IFN α. This reduces the clearance and the decrease of the immunogenicity of the interferon. All of these effects tend to enhance the half-life of the drug.

A large randomised trial in patients without renal failure demonstrated that PEG IFN α is superior to standard IFN α, with respect to sustained virological response, tolerability, and for treatment of HCV-infected patients with cirrhosis, who typically have a poor response to standard IFN α therapy.

There are limited published studies about the use of PEG IFN α in the treatment of HCV infection in dialysis patients. In the first published study, the efficacy of PEG IFN α-2a was evaluated in three HCV-infected dialysis patients [104]. The initial dose (180 µg per week for 48 weeks) was adjusted based upon weekly blood values, with downward dosing determined by decreases in neutophil or platelet count. HCV RNA was undetectable in all three patients after 12 weeks of treatment. Viremia returned in one patient after 24 weeks of treatment, which was considered as a treatment failure. HCV RNA remained undetectable in the other two patients after 48 weeks of treatment and 24 weeks after the treatment finished (SVR).

In another study, twelve HCV RNA-positive dialysis patients received PEG-IFN α -2a (135 µg weekly) for 48 weeks [105]. A sustained viral response was observed in nine patients (75%). Most of the patients experienced several side-effects (anaemia in 75%, fatigue in 58.3%, thrombocytopenia in 33.3% and leucopenia in 33.3%), but there was no discontinuation of the treatment

Pegylated interferon treatment of HCV infection in dialysis patients seems to provide more benefit in terms of viral response, compared to standard interferon monotherapy. At present, therapy with standard or pegylated interferon is advised for HCV infected dialysis patients who are candidates for renal transplantation. [106].

Finally, a great effort should be made to prevent the spread of HCV infection in dialysis units and to understand the natural history of HCV infection in these patients with unique characteristics.

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ХЕПАТИТИС Ц КАЈ ПАЦИЕНТИ НА ДИЈАЛИЗА

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Кај пациентите на дијализа постои висока преваленција на хепати-тис Ц вирусната (ХЦВ) инфекција и истата е главен етиолошки фактор за развивање на црнодробна болест кај истата популација. Во ширењето на ХЦВ инфекцијата поме|у пациентите на дијализа вклучени се повеќе ризик фактори, i toa: бројот на примени трансфузии на крв и крвни деривати, дијализниот стаж на пациентите и преваленцијата на инфекцијата во цен-трите за дијализа.

Препораките за спречување на ширењето на ХЦВ инфекцијата во центрите за дијализа не се спроведуваат во целост, заради ограниченоста на тестовите за идентификација на вирусот, нејасните механизми на трансмисија на вирусот и високата преваленција на ХЦВ инфекцијата во самите центри за дијализа.

Природниот тек на ХЦВ инфекцијата кај пациентите на дијализа с# уште претставува енигма, заради бавната прогресија на црнодробната болест кај тие болни и можноста да не дојде до целосна клиничка експресија на инфекцијата заради нивниот очекуван скратен животен век. Клиничкиот тек на ХЦВ инфекцијата во најголем број случаи е асимптоматски, со бенигна прогресија на црнодробната болест. Но, морталитетот на пациентите на дијализа инфицирани со ХЦВ е повисок во споредба со неинфицираните пациенти, не само како резултат на црнодробното оштетување, туку и како резултат на кардиоваскуларните болести.

Актуелната ХЦВ инфекцијата кај пациентите на дијализа се лекува со интерферон (стандарден или пегелиран), со внимателна селекција на пациентите и со внимателно следење на несаканите ефекти што се јавуваат во текот на лекувањето. Пред трансплантација на бубрег, сите инфицирани пациенти со ХЦВ треба да се лекуваат со интерферон, затоа што ХЦВ инфекцијата влијае негативно на преживувањето на графтот и на пациентот, а од друга страна интерферонот е контраиндициран по трансплантацијата бидејќи предизвикува отфрлање на графтот.

Клучни зборови: Хепатитис Ц вирусна инфекција, дијализа, епидемиологија, дијагноза, превенција, терапија.

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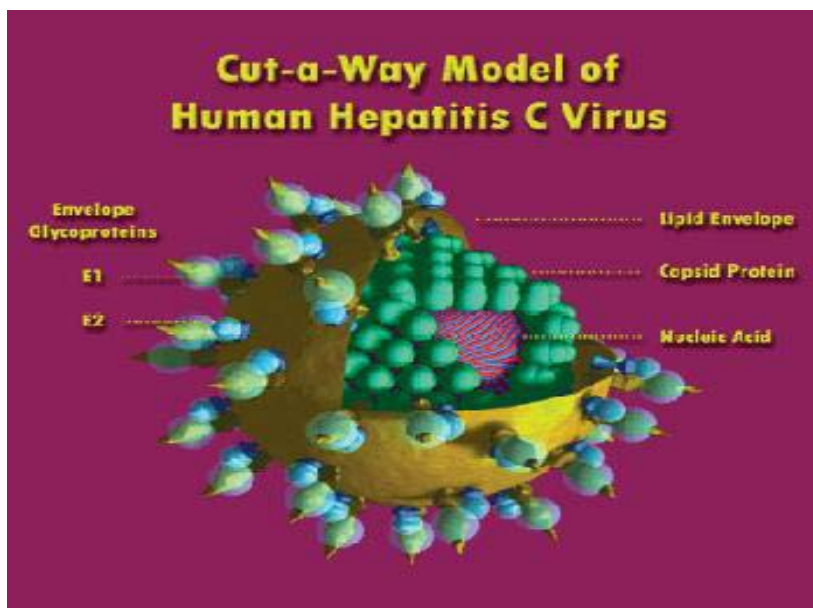
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Figure 1. Cut-a-way model of HCV with the presentation of lipid envelope, envelope glycoprotein (E1 and E2) and nucleotides.

Слика 1. Модел на ХЦВ со презентација на липидната обвивка, гликопротеините во обвивката (Е1 и Е2) и нуклеотидите.

Figure 2. The Natural History of HCV Infection and Its Variability from Person to Person.
The course of infection varies widely among persons. Factors that decrease the risk of progression include female sex and a young-er age at infection; factors that increase the risk include alcohol intake, an older age at infection, male sex, and coinfection with other viruses. Persons with a favorable risk profile often do not have progressive liver disease until 30 or more years after infection. In contrast, 20 percent of persons with chronic hepatitis C will eventually have cirrhosis, and this can occur 20 years or less after infection, especially in those with alcohol abuse or coinfection with human immunodeficiency virus type 1 or hepatitis B virus. Once cirrhosis is established, the risk of hepatocellular carcinoma is 1 to 4 percent per year.
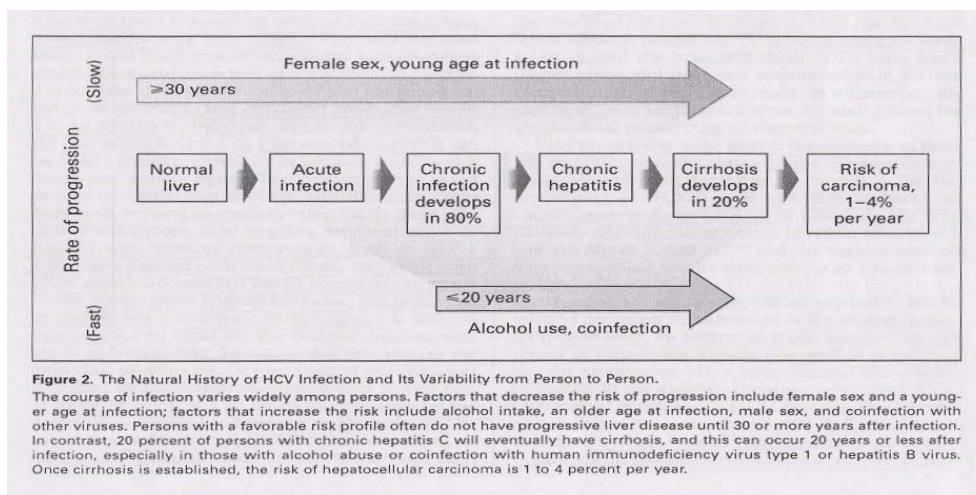
Figure 2. The natural history of HCV infection and its variability from person to person (Lauer, NEJM 2001)
Слика 2. Природен тек на HCV инфекцијата и нејзината варијабилност кај различни индивидуи (Lauer, NEJM 2001)

Table 1. Hepatitis C estimated global prevalence and number infected by WHO region
Табела 1. Глобална преваленција на HCV инфекцијата според Светска Здраствена Оранизација

WHO region	Total population (Millions)	Hepatitis C prevalence rate (%)	Infected population (Millions)	No data available (Number of countries)
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7

Eastern Mediterranean	466	4.6	21.3	5
Europe	858	1.03	8.9	19
South-East Asia	1500	2.15	32.3	3
Western Pacific	1600	3.9	62.2	11
Total	5711	18.7	169.7	57

Table 2. Prevalence of HCV infection in general and dialysis population
Табела 2. Преваленција на HCV инфекцијата во генералната и дијализната популација

Country	Prevalence in general population	Prevalence in dialysis population	reference (year)
Netherlands	0.1%	3%	1998
Italy	0.5%	22.5%	1999
Belgium	0.9%	9.4%	1998
Bulgaria	1.1%	65.8%	1998
France	1.1%	16.3%	2000
Turkey	1.5%	31.4%	1998
USA	1.8%	10%	2003
Saudi Arabia	1.8%	57%	2001
Moldavia	4.9%	75%	1999
Egypt	18.1%	80%	2000

Table 3. Incidence *de novo* of HCV infection in dialysis units
Табела 3 . Инциденција на HCV инфекцјта во центрите за дијализа

	No of units	No of patients	Years	Incidence %

France	25	1323	1997-2000	0,4
Italy	1	72	2000-2003	1,38
Netherlands	9	450	1995-1997	0,5
Spain	7	890	1992-2002	0,5
Tunisia	10	395	2001-2003	0,5
Japan	9	2744	1999-2003	0,33