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Epidemiological and Virological Study of Hepatitis C Virus Infection in Hemodialysis (Case of Six Centers) in Morocco

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Abstract

The purpose of this study was to determine the prevalence of viral RNA and HCV genotypic profile 6 hemodialysis centers in Casablanca. A total of 630 patients were included in this survey, 194 patients of them have antibodies antiHCV + ; then the prevalence is 30.79% , indeed search for viral RNA by PCR in this population was detected in 105 patients , also, the prevalence of viral RNA is 54.1%. The study of genotypic profile in this population showed the following distribution: the most prevalent genotype is genotype 1: subtype 1a was found in 19 patients (18.09%); subtype 1b was found in 49 patients either (46, 66%); genotype 2a / 2c in 27 patients (25.71%); genotype 2 in 5 patients (4.76%), 4h genotype was detected in one patient with a frequency of 0, 95%, genotype 4 was found in 4 patients with a frequency of 3, 80%. Indeed, extensive studies and large scale is needed to understand the epidemiology of HCV.

Keywords: Hepatitis C virus, Prevalence, Genotype, Public health, Morocco genotypes in hemodialysis.

1. Introduction

Virus hepatitis c virus (HCV) was identified in 1989 as the causative agent of most of the previously called hepatitis (non-A non-B parenteral transmission) (Choo QL, *et al.* 1989), the HVC is one of five hepatitis virus (ABCD and E) It is a small virus belonging to the family of Flaviridae wrapped in 55-65 nm the diameter (Kaito, *et al.* 1994). The HCV genome is a single RNA molecule of 9.6 kb positive-strand (Penin, *et al.* 2004) .The HVC has a high genetic diversity, due to the activity lack of exonuclease 5'-3' (lack of corrective activity) RNA-dependent RNA polymerase (Ogata, *et al.* 1991).

The 5'UTR (5' Untranslated Region) is one of the most conserved regions of the genome with more than 90% homology between the sequences of different strains (Bukh, *et al.* 1992). Capsid coding region is also highly conserved from 81 to 88% homology (Simmonds, *et al.* 1994) . The most variable region of the genome is one encoding the envelope proteins E1 and E2. The sequences encoding the hypervariable regions HVR1, HVR2 and HVR3 glycoprotein E2 may vary from 50% of a strain to the other (Choo, *et al.* 1991, Smith 1999, Troesch, *et al.* 2006, Weiner, *et al.* 1991).

To bring order to the overall genetic diversity of HCV, a classification based on molecular phylogenetic analysis of viral sequences was developed, in fact a consensus for a system of nomenclature and classification of variants of HCV genotypes (Simmonds, *et al.* 2005). Each genotype is phylogenetically subdivided into a number of subtypes named alphabetically in the order of their discovery. Thus variants of HCV are classified into six genotypes (representing 6 genetic groups defined by phylogenetic analysis), 72 subtypes have been identified up to now (Simmonds, *et al.* 2005).

As HCV is an RNA virus, it circulates in the host as a viral quasispecies, that is to say, a complex mixture and precariously variant genetically distinct but related (Martell, *et al.* 1992, Farci and Purcell 2000).

In some patients infected with HCV it can be found more than one genotype, this is what we call mixed genotypes infection (Chen, *et al.* 2003, Antonishyn, *et al.* 2005).

HCV genotyping is essential and help us to make epidemiological surveys, clinical and treatment management, indeed genotypes and subtypes vary in worldwide geographical distribution (Zein 2000). Genotypes 1a, 1b, 2 and 3 are more common worldwide; genotype 4 is very present in the Middle East. Genetic diversity contributes to the pathogenesis, genotypes 1 and 4 are more resistant than genotypes 2 or 3 to treatment with Interferon α plus Ribavirin. Duration of treatment is tailored to genotype (Hadziyannis, *et al.* 2004, Fried, *et al.* 2002).

2. Materials and Methods

The present study is a prospective, cross-sectional, multicenter epidemiological study realized.
The purpose of this work is:

- Assess the serological prevalence of HCV.
- Detection of viral RNA by PCR.
- Determine the genotypes and the distribution of types and subtypes in this population by a reverse hybridization assay (LIPA).

This study includes 630 patients chronically infected by HCV and undergoing hemodialysis, in six hemodialysis centers in Casablanca. The epidemiological and clinical Collection has been given by the establishment of a questionnaire: A detailed clinical history and a survey on risk factors have been undertaken.

The study procedure was approved by the Ethics Committee at Pasteur Institute of Morocco, patients involved were informed of the purpose of this survey and a consent form was signed. After the collection of blood in hemodialysis patients (approximately 10 ml were collected), the samples were placed in EDTA tubes, which are transported to the laboratory

Molecular biology at Pasteur Institute storage, packaging has been sterilized in bags. These samples were centrifuged to obtain plasma which is the biological material to be used. The aliquot serum is divided into three tubes, one for serological tests, the other 2 for molecular analysis (PCR and Genotyping) plasmas that are not used immediately and were stored at -20 degrees Celsius.

Serotyping: characterization of antibodies specific for different genotypes:
The anti-HCV antibodies in serum search are carried out by ELISA (enzyme-linked immunosorbent assay) of the third generation.
The subject is considered positive if the antiHCV + ELISA test is positive.

The molecular tests based on the analysis of a region of the viral genome by PCR:
Detection of HCV RNA in the serum is performed by a standard method of reverse transcription followed by a chain reaction amplification of DNA polymerase (RT-PCR).

Our molecular biology laboratory is equipped with Cobas TaqMan HCV Test (Roche) [Cobas Monitor HCV 2.0 (Roche Diagnostics)], which allows the Detection and Quantification of HCV RNA in the serum of patients.

The serum of all patients with positive serology is collected to extract RNA VIRAL according to manufacturer's instructions (Cobas Monitor HCV 2.0 (Roche Diagnostics)], samples of which were not revealed viral RNA are considered as a patients who eliminated HCV: a negative PCR.

The genomic typing: characterization of polymorphism of a genome fragment
The method most widely used to determine the genotype of HCV is the line probe assay commercially available (INNO-LIPA), based on specific oligonucleotides of the 5'-untranslated region (5 'untranslated region) that are immobilized on a nitrocellulose strip, the oligonucleotides are then probed with a 5 'UTR amplicon labeled with biotin, which binds to a specific bands genotype manner; the oligonucleotides are then visualized by using a reaction with streptavidin-peroxidase. The genotype is then identified with an algorithm model.(Stuyver*, et al.* 1993) (Sandres-Saune*, et al.* 2003)

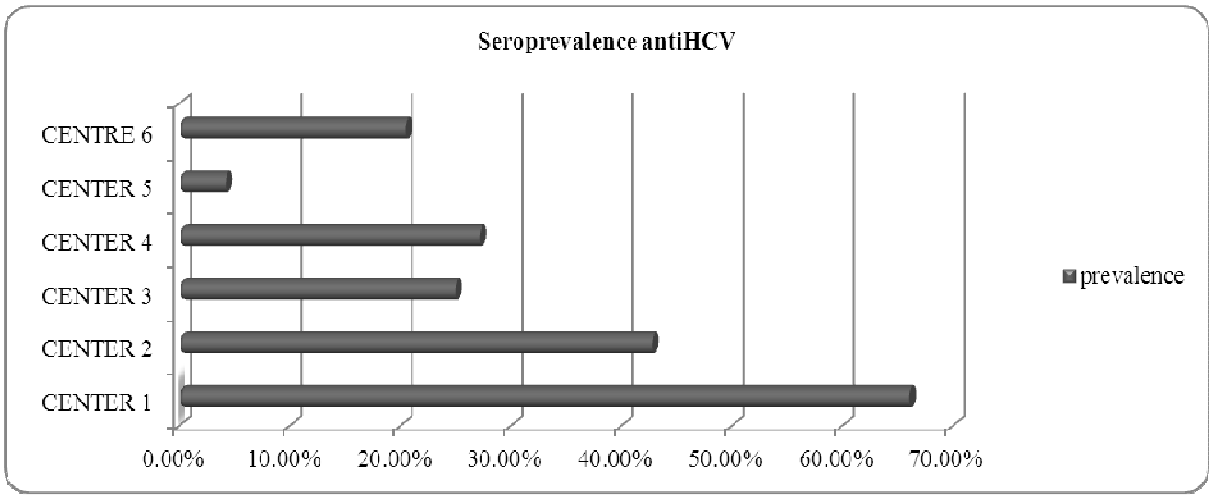
In our study, genotyping was performed on all serum from HCV-RNA positive samples.

3. Results

We conducted this study with all patients (630 patients) in 6 centers hemodialysis , Median age is 48.33 +/- 15.5 years, the range ages is 8-90 years, while the mean age was 48 years, sex male / female ratio of 0.91. No patients included in this study are infected with HIV; two patients are co-infected with HBV.

Statistical analysis showed that the prevalence increases with age, but this is not significant findings. Then, there's no correlation between HCV infection and sex.

Among the 630 patients seeking hemodialysis antiHCV antibodies is positive for all 194 of them, prevalence is 30.79%.



Graphic 1: the frequency of seropositivity of HCV among centers of hemodialysis

4. Discussion

Search for antiHCV by ELISA in 630 patients in 6 centers antibody was positive in 194 patients a prevalence of 30.79%, these results are similar to an earlier study conducted by our research team (Foullous.A, *et al.* 2014).Then; the prevalence of antibodies antiHCV is dramatically high; which can be explained by nosocomial transmission associated with risk factors: duration of dialysis and blood transfusion before 1994 (Foullous.A, *et al.* 2014, Sekkat, *et al.* 2008, Caramelo, *et al.* 1994).

Among the 194 patients; Research From viral HCV RNA revealed the detection of the viral genome in 105 patients then the prevalence is 54.1%.

The prevalence varies considerably from one center to another, indeed centers 1, 2 and 3 have a high prevalence (table 1) explained by a deficiency in structures and lack of personal manager , Centers 1 ,2 and 3 start working before 1994 (blood transfusion problem), other centers 4, 5 and 6 are newer. These results are comparable to one's found in several studies; the prevalence of Viral RNA varies from 58 to 92% of hemodialysis patients chronically infected with HCV antibody (Roth 1995, Stehman-Breen, *et al.* 1998, Espinosa, *et al.* 2001, Natov, *et al.* 1998, Salama, *et al.* 2000).

Table 1: prevalence of viral RNA in the HCV in hemodialysis patients

	PCR +	PCR-	TOTAL PATIENT	PREVALENCE
CENTRE1	56	34	90	62,22%
CENTRE2	23	16	39	58,97%
CENTRE3	9	3	12	75%
CENTRE4	8	22	30	26,6%
CENTRE5	2	5	7	28,57%
CENTRE6	7	9	16	43,75%
TOTAL	105	89	194	54,1%

Our sample was 194 patients; we have detected RNA viral in 105 patients: prevalence is 54.1%.

In this study the results of the genotyping technique by LIPA found that genotype 1b was the most common with a frequency of 46.66% and the genotype 1a/1b (18.09%),genotype 2a/2c (25.71%),genotype 2 (4.76%), genotype 4h (0.95%) and genotype 4 (3.8%).

In Morocco, the first study operated in 1997 found that genotype 1b was predominant in the general population with a frequency 47.6%, followed by genotype 2a / 2c (37.1%) and genotype 1a (2, 8%), while in hemodialysis patients, only one genotype was found with a prevalence of 68.4% for subtype 1b and 15.8% for subtype 1a(Benani, *et al.* 1997) .

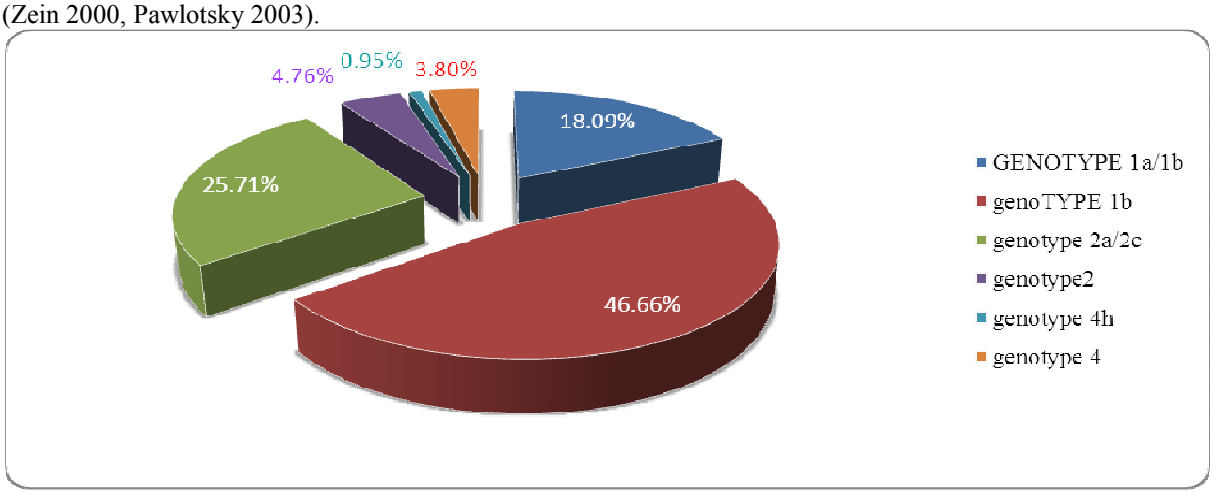
In Moroccan general population a recent study, showed that genotypic distribution is comparable to ours: The results of sequencing the 5'UTR showed the presence of three genotypes 1, 2 and 4. On 174 infected

patients; 122 presented genotype1b (70.1%); 49 presented genotype 2 (28.2%) and (0.6%) non classified (Brahim, *et al.* 2012).

Another study conducted by Rabat team in 2000 found that the distribution of genotypes of HCV genotype 1 (21, 47%), 2a/2c (13, 29%), 1a (6, 13%) and 3 (1,2%)(Cacoub, *et al.* 2000).

Genotype 4 was found in 2 centers, which is not common in MOROCCO, it was found in 5 patients of 105 hemodialysis patients with a frequency of 4.75%, after an investigation ; these patients were infected during their trip to Mecca (pilgrimage).

It seems that the prevalence and incidence of different genotypes of HCV depends on geographic regions and modes of transmission (Wasley and Alter 2000) . Genotypes 1, 2 and 3 are ubiquitous genotypes and they are most common in the world (Bhattacherjee, *et al.* 1995, McOmish, *et al.* 1994, Nousbaum, *et al.* 1995) , genotype 4 is very common in Central Africa, Egypt and Middle East(Ray, *et al.* 2000) . Genotype 5 is predominant in South Africa (Smuts and Kannemeyer 1995). While genotype 6 is present in South- East of Asia (Zein 2000, Pawlotsky 2003).



Graphic 2: variation of HCV genotype in hemdialysis

Results from the genotype analysis shows that the genotype 1b is most common with a 46.66% of frequency; genotypes 1a / 1b (18.09%), genotypes 2a / 2c (25.71%), genotypes 2 (4.76%), genotypes 4h (0.95%) and gynotypes 4 (3.8%).

Determining HCV genotype is very important in order to understand the transmission way. The relationship between genotype and transmission way of infection is well established: patients infected by transfusion are more often infected with genotype 1b (Payan, *et al.* 2005, Laperche, *et al.* 2012). Patients intravenous drug users are mostly infected with genotype 3a (2/3 cases) and 1a (1/3 of cases) (Pawlotsky, *et al.* 1995, Schroter, *et al.* 2004, Trimbitas, *et al.* 2014).

Nowadays, the genotype of HCV remains the main predictor of sustained virologic response (Suppiah, *et al.* 2009, Tanaka, *et al.* 2009). With all treatments tested up to now, patients with genotypes 2 and 3 are twice as likely as patients with genotype 1 for a sustained virologic response (McHutchison, *et al.* 1998, Manns, *et al.* 2001). Indeed, when using the combination of Interferon and Ribavirin, patients with genotypes 2 or 3 are treated for only 24 weeks, while it is recommended that patients infected with genotype 1 receive treatment for 48 weeks. Although an inhibitor of HCV protease is added to the treatment protocol is also affected by the genotype (Lee, *et al.* 2008).

5. Conclusion

The study of viral diversity provides a better understanding of the epidemiology of HCV infection, the origin and dynamics of viral infections. Epidemiological studies all over the world show that the distribution of HCV genotype is characteristic of each region.

In our series, the prevalence varies between 66.1% and 4.2% depending on the center, with an average of 30.79%, this high seroprevalence can be explained by risk factors in hemodialysis: vascular, the immunodepresion hemodialysis patients, blood transfusion and duration of dialysis. The detction of viral ARN showed an average prevalence of 54.1%. While the Results from the genotype analysis shows that the genotype 1b is most common with a 46.66% of frequency; genotypes 1a / 1b (18.09%), genotypes 2a / 2c (25.71%), genotypes 2 (4.76%), genotypes 4h (0.95%) and gynotypes 4 (3.8%). The HCV have a high genetic diversity. This one is caused by non attendance of exonuclease activity resulting from 5'-3 '(lack of corrective activity) of ARN polymérase dependent RNA, but also the high level of replication (10x12000 new HCV virions per day) then a genetic variability is estimated to 1.9x10000 per site per year(Ogata, *et al.* 1991, Smith, *et al.* 1997, Neumann, *et al.* 1998) .

This variability is involved in treatment response, it's one main obstacles development of a vaccine, determing HCV genotype is very important in order to understand the transmission way

Genotyping is essential since genotypes 1 and 4 are more resistant to treatment than genotypes 2 or 3 with treatment combination pegylated Interferon α (pegIFNα) plus Ribavirin (RBV) and also the duration of treatment is tailored to each genotype.

Other studies should be undertaken to study the dynamics of change over time and to identify mutations in the protein coding region of the capsid in order to understand the mechanisms of viral persistence and resistance to antiviral drugs and to study the geographical distribution of genotypes and subtypes circulating HCV in different hemodialysis centers.

References

Choo QL, Kuo G, Weiner AJ, Overky LR, Bradley DW and H. M.(1989),"1989 Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome.",*Science* 244(359-362

M. Kaito, S. Watanabe, K. Tsukiyama-Kohara, K. Yamaguchi, Y. Kobayashi, M. Konishi, M. Yokoi, S. Ishida, S. Suzuki and M. Kohara.(1994),"Hepatitis C virus particle detected by immunoelectron microscopic study",*J Gen Virol* 75 (Pt 7)(1755-60

F. Penin, J. Dubuisson, F. A. Rey, D. Moradpour and J. M. Pawlotsky.(2004),"Structural biology of hepatitis C virus",*Hepatology* 39(1),5-19

N. Ogata, H. J. Alter, R. H. Miller and R. H. Purcell.(1991),"Nucleotide sequence and mutation rate of the H strain of hepatitis C virus",*Proc Natl Acad Sci U S A* 88(8),3392-6

J. Bukh, R. H. Purcell and R. H. Miller.(1992),"Sequence analysis of the 5' noncoding region of hepatitis C virus",*Proc Natl Acad Sci U S A* 89(11),4942-6

P. Simmonds, D. B. Smith, F. McOmish, P. L. Yap, J. Kolberg, M. S. Urdea and E. C. Holmes.(1994),"Identification of genotypes of hepatitis C virus by sequence comparisons in the core, E1 and NS-5 regions",*J Gen Virol* 75 (Pt 5)(1053-61

Q. L. Choo, K. H. Richman, J. H. Han, K. Berger, C. Lee, C. Dong, C. Gallegos, D. Coit, R. Medina-Selby, P. J. Barr and et al.(1991),"Genetic organization and diversity of the hepatitis C virus",*Proc Natl Acad Sci U S A* 88(6),2451-5

D. B. Smith.(1999),"Evolution of the hypervariable region of hepatitis C virus",*J Viral Hepat* 6 Suppl 1(41-6

M. Troesch, I. Meunier, P. Lapierre, N. Lapointe, F. Alvarez, M. Boucher and H. Soudeyns.(2006),"Study of a novel hypervariable region in hepatitis C virus (HCV) E2 envelope glycoprotein",*Virology* 352(2),357-67

A. J. Weiner, M. J. Brauer, J. Rosenblatt, K. H. Richman, J. Tung, K. Crawford, F. Bonino, G. Saracco, Q. L. Choo, M. Houghton and et al.(1991),"Variable and hypervariable domains are found in the regions of HCV corresponding to the flavivirus envelope and NS1 proteins and the pestivirus envelope glycoproteins",*Virology* 180(2),842-8

P. Simmonds, J. Bukh, C. Combet, G. Deléage, N. Enomoto, S. Feinstone, P. Halfon, G. Inchauspé, C. Kuiken and G. Maertens.(2005),"Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes",*Hepatology* 42(4),962-973

M. Martell, J. I. Esteban, J. Quer, J. Genesca, A. Weiner, R. Esteban, J. Guardia and J. Gomez.(1992),"Hepatitis C virus (HCV) circulates as a population of different but closely related genomes: quasispecies nature of HCV genome distribution",*J Virol* 66(5),3225-9

P. Farci and R. H. Purcell.(2000),"Clinical significance of hepatitis C virus genotypes and quasispecies",*Semin Liver Dis* 20(1),103-26

Y. D. Chen, M. Y. Liu, W. L. Yu, J. Q. Li, Q. Dai, Z. Q. Zhou and S. G. Tisminetzky.(2003),"Mix-infections with different genotypes of HCV and with HCV plus other hepatitis viruses in patients with hepatitis C in China",*World J Gastroenterol* 9(5),984-92

N. A. Antonishyn, V. M. Ast, R. R. McDonald, R. K. Chaudhary, L. Lin, A. P. Andonov and G. B. Horsman.(2005),"Rapid genotyping of hepatitis C virus by primer-specific extension analysis",*J Clin Microbiol* 43(10),5158-63

N. N. Zein.(2000),"Clinical significance of hepatitis C virus genotypes",*Clin Microbiol Rev* 13(2),223-35

S. J. Hadziyannis, H. Sette, Jr., T. R. Morgan, V. Balan, M. Diago, P. Marcellin, G. Ramadori, H. Bodenheimer, Jr., D. Bernstein, M. Rizzetto, S. Zeuzem, P. J. Pockros, A. Lin, A. M. Ackrill and P. I. S. Group.(2004),"Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose",*Ann Intern Med* 140(5),346-55

M. W. Fried, M. L. Shiffman, K. R. Reddy, C. Smith, G. Marinos, F. L. Goncales, Jr., D. Haussinger, M. Diago, G. Carosi, D. Dhumeaux, A. Craxi, A. Lin, J. Hoffman and J. Yu.(2002),"Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection",*N Engl J Med* 347(13),975-82

L. Stuyver, R. Rossau, A. Wyseur, M. Duhamel, B. Vanderborght, H. Van Heuverswyn and G. Maertens.(1993),"Typing of hepatitis C virus isolates and characterization of new subtypes using a line probe

assay",*J Gen Virol* 74 (Pt 6)(1093-102
K. Sandres-Saune, P. Deny, C. Pasquier, V. Thibaut, G. Duverlie and I. J.(2003),"Determining hepatitis C genotype by analyzing the sequence of the NS5b region",*Journal of virological methods* 109(2),187-193
Foullous.A, M.Sobh, M.Lemrini, F.Ouaddi, S.Mahmal, S.Khyate, G.Medkouri, F.Lazar, A.Hammoumi and A.Bennani.(2014),"Prevalence and risk factors of hepatitis C virus among
hemodialysis patients in hemodialysis center",*research and reviews in biosciences* 8(2),48-53
S. Sekkat, N. Kamal, B. Benali, H. Fellah, K. Amazian, A. Bourquia, A. El Kholti and A. Benslimane.(2008),"[Prevalence of anti-HCV antibodies and seroconversion incidence in five haemodialysis units in Morocco]",*Nephrol Ther* 4(2),105-10
C. Caramelo, S. Navas, M. L. Alberola, T. Bermejillo, A. Reyero and V. Carreno.(1994),"Evidence against transmission of hepatitis C virus through hemodialysis ultrafiltrate and peritoneal fluid",*Nephron* 66(4),470-3
D. Roth.(1995),"Hepatitis C virus: the nephrologist's view",*Am J Kidney Dis* 25(1),3-16
Stehman-Breen, C. O., S. Emerson, D. Gretch and R. J. & Johnson.(1998),"Risk of death
among chronic dialysis patients infected with hepatitis C virus",*American journal of kidney diseases* 32(4),629-634
M. Espinosa, A. Martin-Malo, M. A. Alvarez de Lara and P. Aljama.(2001),"Risk of death and liver cirrhosis in anti-HCV-positive long-term haemodialysis patients",*Nephrol Dial Transplant* 16(8),1669-74
S. N. Natov, J. Y. Lau, B. A. Bouthot, B. V. Murthy, R. Ruthazer, C. H. Schmid, A. S. Levey and B. J. Pereira.(1998),"Serologic and virologic profiles of hepatitis C infection in renal transplant candidates. New England Organ Bank Hepatitis C Study Group",*Am J Kidney Dis* 31(6),920-7
G. Salama, L. Rostaing, K. Sandres and J. Izopet.(2000),"Hepatitis C virus infection in French hemodialysis units: a multicenter study",*J Med Virol* 61(1),44-51
A. Benani, J. El-Turk, S. Benjelloun, S. Sekkat, S. Nadifi, N. Hda and A. Benslimane.(1997),"HCV genotypes in Morocco",*J Med Virol* 52(4),396-8
I. Brahim, A. Akil, M. Mtairag el, R. Pouillot, A. E. Malki, S. Nadir, R. Alaoui, R. Njouom, P. Pineau, S. Ezzikouri and S. Benjelloun.(2012),"Morocco underwent a drift of circulating hepatitis C virus subtypes in recent decades",*Arch Virol* 157(3),515-20
P. Cacoub, V. Ohayon, S. Sekkat, B. Dumont, A. Sbai, F. Lunel, A. Benslimane, P. Godeau and M. I. Archane.(2000),"[Epidemiologic and virologic study of hepatitis C virus infections in Morocco]",*Gastroenterol Clin Biol* 24(2),169-73
A. Wasley and M. J. Alter.(2000),"Epidemiology of hepatitis C: geographic differences and temporal trends",*Semin Liver Dis* 20(1),1-16
V. Bhattacherjee, L. E. Prescott, I. Pike, B. Rodgers, H. Bell, A. R. El-Zayadi, M. C. Kew, J. Conradie, C. K. Lin, H. Marsden and et al.(1995),"Use of NS-4 peptides to identify type-specific antibody to hepatitis C virus genotypes 1, 2, 3, 4, 5 and 6",*J Gen Virol* 76 (Pt 7)(1737-48
F. McOmish, P. L. Yap, B. C. Dow, E. A. Follett, C. Seed, A. J. Keller, T. J. Cobain, T. Krusius, E. Kolho, R. Naukkarinen and et al.(1994),"Geographical distribution of hepatitis C virus genotypes in blood donors: an international collaborative survey",*J Clin Microbiol* 32(4),884-92
J. B. Nousbaum, S. Pol, B. Nalpas, P. Landais, P. Berthelot and C. Brechot.(1995),"Hepatitis C virus type 1b (II) infection in France and Italy. Collaborative Study Group",*Ann Intern Med* 122(3),161-8
S. C. Ray, R. R. Arthur, A. Carella, J. Bukh and D. L. Thomas.(2000),"Genetic epidemiology of hepatitis C virus throughout egypt",*J Infect Dis* 182(3),698-707
H. E. Smuts and J. Kannemeyer.(1995),"Genotyping of hepatitis C virus in South Africa",*J Clin Microbiol* 33(6),1679-81
J. M. Pawlotsky.(2003),"Hepatitis C virus genetic variability: pathogenic and clinical implications",*Clin Liver Dis* 7(1),45-66
C. Payan, F. Roudot-Thoraval, P. Marcellin, N. Bled, G. Duverlie, I. Fouchard-Hubert, P. Trimoulet, P. Couzigou, D. Cointe, C. Chaput, C. Henquell, A. Abergel, J. M. Pawlotsky, C. Hezode, M. Coude, A. Blanchi, S. Alain, V. Loustaud-Ratti, P. Chevallier, C. Trepo, V. Gerolami, I. Portal, P. Halfon, M. Bourliere, M. Bogard, E. Plouvier, C. Laffont, G. Agius, C. Silvain, V. Brodard, G. Thiefin, C. Buffet-Janvresse, G. Riachi, F. Grattard, T. Bourlet, F. Stoll-Keller, M. Doffoel, J. Izopet, K. Barange, M. Martinot-Peignoux, M. Branger, A. Rosenberg, P. Sogni, M. L. Chaix, S. Pol, V. Thibault, P. Opolon, A. Charrois, L. Serfaty, B. Fouqueray, J. D. Grange, J. J. Lefrere and F. Lunel-Fabiani.(2005),"Changing of hepatitis C virus genotype patterns in France at the beginning of the third millenium: The GEMHEP GenoCII Study",*J Viral Hepat* 12(4),405-13
S. Laperche, A. Servant-Delmas, P. Gallian and J. Pillonel.(2012),"La surveillance de la diversité des virus VIH, VHB et VHC chez les donneurs de sang français entre 2000 et 2010",*Bulletin Epidémiologique Hebdomadaire [Bull Epidemiol Hebd]* 39-40
J.-M. Pawlotsky, L. Tsakiris, F. Roudot-Thoraval, C. Pellet, L. Stuyver, J. Duval and D. Dhumeaux.(1995),"Relationship between hepatitis C virus genotypes and sources of infection in patients with

chronic hepatitis C",*Journal of Infectious Diseases* 171(6),1607-1610
M. Schroter, B. Zollner, R. Laufs and H. H. Feucht.(2004),"Changes in the prevalence of hepatitis C virus genotype among injection drug users: a highly dynamic process",*J Infect Dis* 190(6),1199-200; author reply 1200-1
R.-D. Trimbitas, F. Z. Serghini, F. Lazaar, W. Baha, A. Foullous, M. Essalhi, A. El Malki, A. M. Bellefquih and A. Bennani.(2014),"The “hidden” epidemic: a snapshot of Moroccan intravenous drug users",*Virology journal* 11(1),43
V. Suppiah, M. Moldovan, G. Ahlenstiel, T. Berg, M. Weltman, M. L. Abate, M. Bassendine, U. Spengler, G. J. Dore, E. Powell, S. Riordan, D. Sheridan, A. Smedile, V. Fragomeli, T. Muller, M. Bahlo, G. J. Stewart, D. R. Booth and J. George.(2009),"IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy",*Nat Genet* 41(10),1100-4
Y. Tanaka, N. Nishida, M. Sugiyama, M. Kurosaki, K. Matsuura, N. Sakamoto, M. Nakagawa, M. Korenaga, K. Hino, S. Hige, Y. Ito, E. Mita, E. Tanaka, S. Mochida, Y. Murawaki, M. Honda, A. Sakai, Y. Hiasa, S. Nishiguchi, A. Koike, I. Sakaida, M. Imamura, K. Ito, K. Yano, N. Masaki, F. Sugauchi, N. Izumi, K. Tokunaga and M. Mizokami.(2009),"Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C",*Nat Genet* 41(10),1105-9
J. G. McHutchison, S. C. Gordon, E. R. Schiff, M. L. Shiffman, W. M. Lee, V. K. Rustgi, Z. D. Goodman, M. H. Ling, S. Cort and J. K. Albrecht.(1998),"Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group",*N Engl J Med* 339(21),1485-92
M. P. Manns, J. G. McHutchison, S. C. Gordon, V. K. Rustgi, M. Shiffman, R. Reindollar, Z. D. Goodman, K. Koury, M. Ling and J. K. Albrecht.(2001),"Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial",*Lancet* 358(9286),958-65
C. M. Lee, C. H. Hung, S. N. Lu and C. S. Changchien.(2008),"Hepatitis C virus genotypes: clinical relevance and therapeutic implications",*Chang Gung Med J* 31(1),16-25
D. B. Smith, S. Pathirana, F. Davidson, E. Lawlor, J. Power, P. L. Yap and P. Simmonds.(1997),"The origin of hepatitis C virus genotypes",*J Gen Virol* 78 (Pt 2)(321-8
A. U. Neumann, N. P. Lam, H. Dahari, D. R. Gretch, T. E. Wiley, T. J. Layden and A. S. Perelson.(1998),"Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy",*Science* 282(5386),103-7

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