Introduction

HCV is a major cause of hepatitis and liver cancer globally, chronically infecting nearly 3% of the world`s population ***(World Health Organization (WHO), 1999).*** During the second half of 20th century, the global HCV pandemic widespread viral transmission was by blood or blood derived products and unsafe medical practice ***(Trepo and Pradat, 1999).***

Today, needle sharing among injecting drug user (IDUs) is a major risk factor in industrialized countries ***(Trepo and Pradat, 1999)*** and prevalence among IDUs ranges from 30 % to 90% ***(Mathei et al., 2008).*** Approximately 15 - 40% of infected persons clear the virus during the acute phase, and nearly 80% result in chronic infections which may lead to subsequent viral transmission ***(Villano et al., 1999).***

Nosocomial HCV transmission during dialysis, colonoscopy and surgery has also been reported ***(Lauer et al., 2001).*** The rate of HCV sero-conversion among health care workers after a needle stick injury is 0 to 7 % ***(Centers for Disease Control (CDC), 1997).*** Perinatal and sexual transmission of the virus is inefficient, but occurs more frequently if the HCV-infected mother or sexual partner is also infected with Human Immunodeficiency Virus (HIV) type 1 ***(Zannetti et al., 1999).*** A variety of epidemiological data provides evidence for the occurrence of nosocomial

transmission of HCV infection to Hemodialysis patients. The most important factor implicated in HCV transmission between patients treated in the same dialysis unit is cross-contamination from supplies and surfaces as a result of failure of staff to follow infection control procedures. Dialyzer reuse was not identified as a risk factor for HCV acquisition in multicenter database ***(Fabrizi et al., 2002).***

The initial test used to diagnose HCV is enzyme immunoassay (EIA), for anti-HCV immunoglobulin G (IgG). The HCV genome encodes a polyprotein of 3,011 to 3,033 amino acids that is processed into 10 structured and non-structured proteins**.** Three generations of screening EIAs have been developed to detect antibodies against various epitops of these proteins ***(Bendinelli et al., 2000).***

The most widely used serologic test is the third generation EIA. The predictive value of this assay is greatest in high risk population, but the false positive rate can be as high as 50%-60% in low risk population ***(Gretch, 1997).***

HCV infection is confirmed by using the combination of a HCV antibody test, which implies previous infection if positive, and Polymerase Chain Reaction (PCR) to detect HCV RNA, which implies ongoing infection if positive ***(Charles et al., 2003).*** The most commonly used virologic assay for HCV is PCR assay which permits detection of a small amount of HCV RNA is serum and tissue samples within days of infection ***(Yagizi and Ballstreri, 2012).***

A Belgian prospective multicenter study showed a reduction from 1.4% to 0 % in the annual incidence of sero-conversion for HCV without any isolation measures, by implementation of strict infection control procedures designed to prevent transmission of blood born pathogens including HCV ***(Fabrizi et al., 2002).***

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. It is a major global health problem and the most serious type of viral hepatitis. It can cause chronic liver disease and puts people at high risk of death from cirrhosis of the liver and liver cancer ***(WHO, 2011).***

Hepatitis B virus is transmitted between people by direct blood-to-blood contact or semen and vaginal fluid of an infected person. In developing countries, common modes of transmission are: perinatal (from mother to baby at birth), early childhood infections (inapparent infection through close interpersonal contact with infected household contacts), unsafe injection practices, unsafe blood transfusions and unprotected sexual contact ***(WHO, 2011).***

In many developed countries (e.g. those in Western Europe and North America), patterns of transmission are different from those in developing countries. The majority of infections in developed countries are transmitted during young adulthood by sexual activity and injecting drug use. Hepatitis B is a major infectious occupational hazard of health workers. The hepatitis B virus is not spread by contaminated food or water, and cannot be spread casually in the workplace ***(WHO, 2011).***

It is well known that hemodialysis patients are at high risk of acquiring parenterally transmitted infections, not only because of the large number of blood transfusions that they receive and the invasive procedures that they undergo, but also because of their immunosuppressed state ***(Alter, 1986)***.

Hepatitis B vaccine has been available since 1982. Use of the vaccine has resulted in a greater than three-fold reduction in the number of new cases since that time. CDC recommends routine vaccination for persons under 18 years age or members of risk groups of any age ***(Toder, 2009)***.

Antibody responses, measured as the surface antibody level (HepBsAb), should be checked 8 weeks after completion of the course of vaccine. The optimum response to vaccination is to achieve Anti-HepBsAb titres above100iu/ml. If the antibody level is greater than100 iu/ml, antibody levels should be repeated annually. If Anti-HepBsAb titre drops below 10iu/ml, on annual testing, a booster dose of the vaccine should be readministered and annual testing continued. Retesting after a booster is not necessary. If Anti-HepBsAb are between 10-99iu/ml, an immediate booster dose of the vaccine should be administered and the anti-HepBsAb level rechecked after 8 weeks. If greater than 10 iu/ml, this indicates an adequate response. Anti-HepBsAb titres should be checked annually from then on. If Anti-HepBsAb titres are less than 10iu/ml after repeating course of vaccination, the patient should be regarded as susceptible to HBV infection and tested for HBsAg on a monthly basis in haemodialysis or at each clinic attendance if on home based renal replacement therapies ***(K/DOQI, 2002).***

Aim of the Work

1. To determine the prevalence of HBV and HCV infection among pediatric patients on regular hemodialysis.
2. To determine the immune status and response to HBV vaccination among pediatric patients on regular hemodialysis.

Chapter (1)

Hepatitis C Virus Overview

Hepatitis C virus (HCV) is a major cause of progressive liver disease with approximately 130-170 million people infected worldwide. HCV induces chronic infection in up to 80% of infected individuals. The main complications of HCV infection are severe liver fibrosis and cirrhosis, and 30-50% of individuals with cirrhosis go on to develop hepatocellular carcinoma ***(Alter et al., 1999).***

Epidemiology:

In the United States, antibodies to HCV are present in approximately 0.2 percent of children ages 6 to 12 and in 0.4 percent of those ages 12 to 19, rates that are similar to the prevalence observed in volunteer adult blood donors but that are lower than adult prevalence based upon National Health and Nutrition Examination survey data ***(Armstrong et al., 2006).***

The proportion of children who are HCV antibody-positive who are also HCV RNA positive is not known precisely; based upon studies in adults, it is estimated to be approximately 75 to 80 percent ***(Delgado et al., 2012).***

The prevalence is much higher (50 to 95 percent) in individuals who received blood products for conditions such as thalassemia or hemophilia before 1990 to as late as 1992 ***(Resti***

et al., 1992). Seroprevalence rates of 10 to 20 percent have been reported among children with a variety of other potential exposures such as malignancy, hemodialysis, extracorporeal membrane oxygenation, or surgery for congenital heart disease ***(Murray et al., 2003).***

The burden of disease due to chronic viral hepatitis constitutes a global threat. In many countries, the burden of chronic liver disease due to hepatitis B and C is increasing due to ageing of unvaccinated populations and migration, and a probable increase in drug injecting. Targeted vaccination strategies for hepatitis B virus (HBV) among risk groups and harm reduction interventions at adequate scale and coverage for injecting drug users are needed. Transmission of HBV and hepatitis C virus (HCV) in healthcare settings and a higher prevalence of HBV and HCV among recipients of blood and blood products in the Balkan and North African countries highlight the need to implement and monitor universal precautions in these settings. Progress in drug discovery has improved outcomes of treatment for both HBV and HCV, although access is limited by the high costs of these drugs and resources available for health care ***(Esmat et al., 2013).***

Men were somewhat higher educated than women about modes in which hepatitis C virus can be transmitted. Seventy-nine percent of men knowing about hepatitis C were able to name at least one way in which the virus can be transmitted. Similar to the pattern observed for women, the three modes of

transmission mentioned most often by men were blood transfusions (81 %), use of unclean needles (71 %), and other contact with the blood of an infected person (54 %). Around one in six men also mentioned having sexual relations with an infected person or having other physical contacts as ways in which hepatitis C may be transmitted ***(EDHS, 2008)***.

There appears to be worldwide geographic variation in the prevalence of HCV infection in children, the reasons for which are incompletely understood. Studies in the early 1990s reported prevalence rates ranging from 0 percent in Japan and Taiwan ***(Tanaka et al., 1992);*** 0.4 percent in Italy ***(Gessoni and Manoni, 1993);*** 0.6 percent in Malaysia ***(Lee and Ng, 2001);*** 0.9 percent in Saudi Arabia ***(Al-Faleh et al., 1991);*** 1.4 percent in Moldova ***(Drobeniuc et al., 1999);*** and up to 14.5 percent in Cameroon ***(Ngatchu et al., 1992).*** Prevalence rates in Egypt were low in the 1990s among children without a history of exposure to blood products ***(Khalifa et al., 1993),*** but a more recent series reported HCV rates of 2 percent ***(El-Raziky et al., 2007).*** 49.3-64.0 million adults in Asia, Australia and Egypt are anti-HCV positive. China alone has more HCV infections than all of Europe or the Americas. While most countries had prevalence rates from 1 to 2% we documented several with relatively high prevalence rates, including Egypt (15%), Pakistan (4.7%) and Taiwan (4.4%) ***(Esmat et al., 2011).***

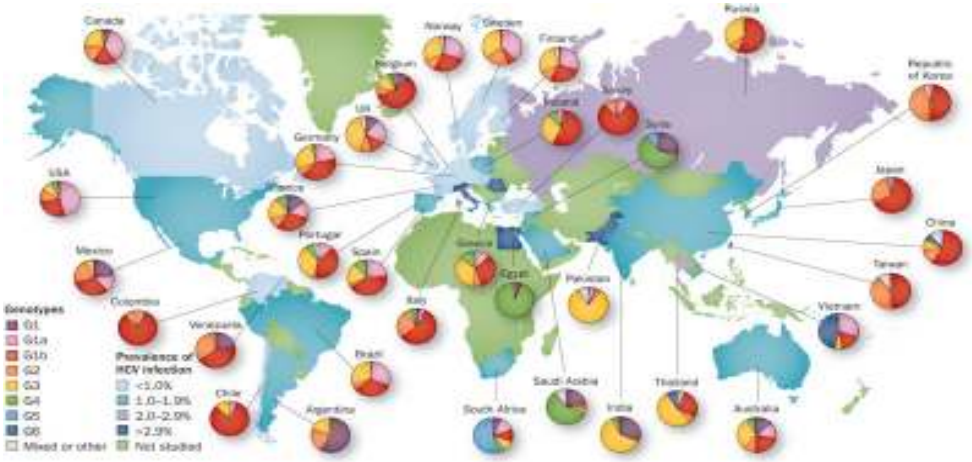

Figure (1): Shows prevalence of HCV infection and distribution of its different genotypes ***(WHO, 2011).***

Overall, approximately 28,000 new HCV infections occur in the United States each year, although the specific incidence in children is unknown ***(Alter, 1997).***

Although surgical interventions and blood transfusion are significant risk factors for HCV acquisition in Egyptian children, dental treatment remains the highest risk factor for HCV chronic persistence in children ***(Esmat et al., 2012).***

Viral Genome and Replication:

HCV is closely related to flaviviruses and pestiviruses. Although its diversity is great enough for it to be classified as a separate genus. The hepatitis C virus particle consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid (fatty) envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope ***(Beeck and Dubuisson, 2003).***

The HCV genome is a positive-sense RNA molecule of approximately 9500 nucleotides. There are highly conserved 5' and 3' untranslated regions flanking an approximately 9000 nucleotide single open reading frame which encodes a large polyprotein of about 3000 amino acids ***(Jhaveri, 2011)***.

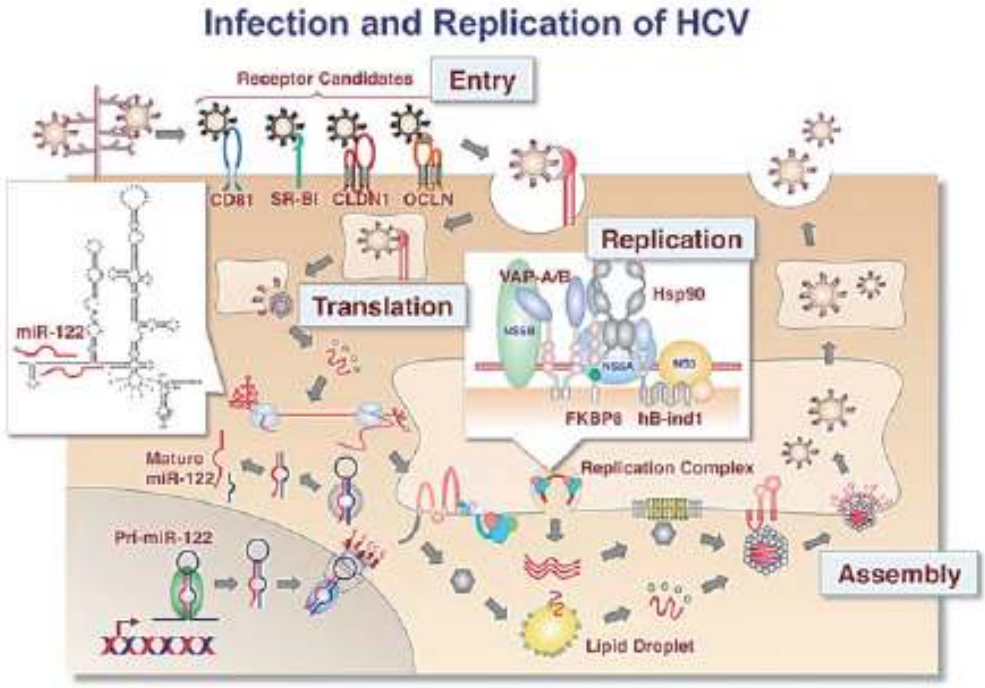

Figure (2): Above shows replication of HCV inside the infected cell ***(Rinonce et al., 2013).***

Replication of HCV involves several steps. The virus replicates mainly in the hepatocytes, where it is estimated that daily calculated total of one trillion virions generated. The virus may also replicate in peripheral blood mononuclear cells, potentially accounting for the high levels of immunological disorders found in chronically infected HCV patients. HCV has a wide variety of genotypes and mutates rapidly due to a high error rate on the part of the virus' RNA-dependent RNA

polymerase. The mutation rate produces so many variants of the virus it is considered a quasispecies rather than a conventional virus species ***(Bartenschlager and Lohmann, 2000).*** Entry into host cells occur through complex interactions between virions and cell-surface molecules CD81, LDL receptor, SR-BI, DC-SIGN, Claudin-1, and Occludin ***(Zeisel et al., 2009).***

The virus replicates on intracellular lipid membranes ***(Dubuisson et al., 2002).*** The endoplasmic reticulum in particular are deformed into uniquely shaped membrane structures termed 'membranous webs'. These structures can be induced by sole expression of the viral protein NS4B ***(Egger et al., 2002).*** The core protein associates with lipid droplets and utilises microtubules and dyneins to alter their location to a perinuclear distribution ***(Boulant et al., 2008).*** Release from the hepatocyte may involve the very low density lipoprotein secretory pathway ***(Syed et al., 2010).***

Viral Heterogeneity:

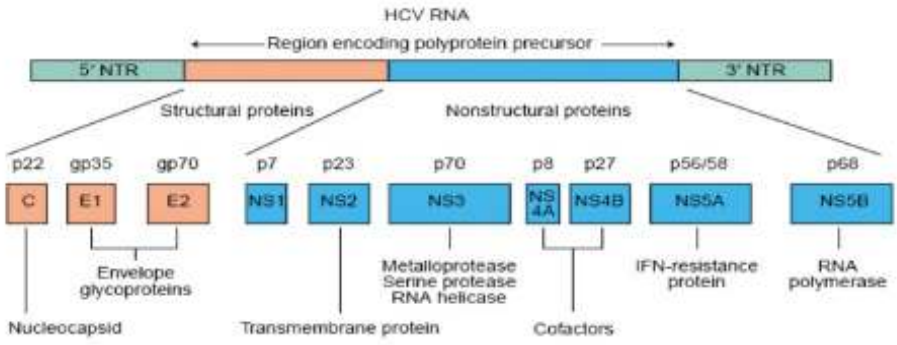

Figure (3): Shows the different genotypes of HCV ***(Rinonce et al., 2013).***

The polymerase enzyme of RNA viruses such as HCV lacks proofreading ability and is therefore unable to correct copying errors made during viral replication. Many of these nucleotide changes result in a nonfunctional genome or a replication incompetent virus (lethal mutants). However, others persist and account for the tremendous viral diversity that is characteristic of HCV. This heterogeneity is extremely important in the diagnosis of infection, pathogenesis of disease, and the response to treatment; it prevents the development of conventional vaccines, allows the virus to escape eradication by the host's immune system, and affects the completeness of the response to antiviral therapies such as interferon. This genetic diversity of HCV may allow it to escape host immune surveillance, thereby resulting in virus persistence and a lack of protective immunity ***(Armstrong, 2006).***

Transmission:

Most patients infected with HCV in the United States and Europe acquired the disease through intravenous drug use or blood transfusion, the latter of which has become rare since routine testing of the blood supply for HCV was begun in 1990. Other types of parenteral exposure are important in specific regions in the world ***(Khalifa et al., 1993).***

Some of these risk factors were elucidated in a case control study from the United States involving 2316 HCV positive blood donors in whom the following HCV risk factors were identified ***(Lee et al., 1991)****:*

- Intravenous drug use.
- Blood transfusion.

- Sex with an intravenous drug user. .
- Religious scarification.
- Having been struck or cut with a bloody object.
- Pierced ears or body parts.
- Immunoglobulin injection.

Illicit drug use: Parenteral exposure to the hepatitis C virus is the most efficient means of transmission. Thus, it is not surprising that injection drug use with shared needles or other paraphernalia has been the most common identifiable source of acute HCV infection in the United States ***(Gessoni and Manoni, 1993).***

Hemodialysis: The incidence and prevalence of HCV infection among patients on dialysis has steadily declined in recent years. Among member nations in the European Dialysis and Transplant Association, for example, the prevalence of anti-HCV declined from 21 percent in 1992 to 17.7 percent in 1993**.** Nonetheless, the 0.4 to 15 percent incidence of anti-HCV positivity in hemodialysis units continues to be a cause for concern. A number of risk factors have been identified for HCV infection among dialysis patients, including blood transfusions, the duration of end-stage renal disease (and dialysis), the type of dialysis (risk is highest with in-hospital hemodialysis and lowest with peritoneal dialysis), and the prevalence of HCV infection in the dialysis unit ***(Ceci et al., 2001).***

Organ transplantation: Transplant recipients who receive organs from HCV-positive donors have a high risk of acquiring HCV infection and liver disease ***(Mohan et al., 2007).***

Blood transfusion: Blood transfusion was a major risk factor for acute infection in the past, with more than 10 percent of transfusion recipients acquiring infection in some studies ***(Drobeniuc et al., 1999).*** The screening of blood donors for historical risk factors, serologic evidence of hepatitis B infection (HBsAg and anti-HBc), and elevated serum ALT caused a striking reduction in the rates of non-A, non-B post-transfusion hepatitis, even before HCV was identified ***(Ngatchu et al., 1992).***

Hospitalization: Nosocomial transmission of HCV has been documented in several health care settings. It is possible that transmission during hospitalization was due to unsafe medication injection practices ***(Vogt et al., 1999).***

Perinatal transmission: Perinatal transmission of HCV occurs at the time of birth in about 5 percent of infants born to anti-HCV positive women ***(Aricò et al., 1994).*** The risk of infection is approximately twofold higher in infants born to women coinfected with HCV and HIV ***(Locasciulli et al., 1997).*** Transmission occurs almost exclusively from mothers who are HCV-RNA positive (as opposed to those who are anti-HCV positive but HCV-RNA negative), the risk of transmission is, like HIV, in part related to the level of viremia at the time of birth ***(Strickland et al., 2000).***

Clinical Features and Natural History:

HCV causes both acute and chronic hepatitis. The incubation period ranges from 14-180 days (average: 6-7 weeks). Persons with newly acquired (acute) HCV infection typically are either asymptomatic or have a mild clinical illness. The course of acute hepatitis C is variable, although elevations in serum alanine aminotransferase (ALT) levels, often in a fluctuating pattern, are the most characteristic feature. Fulminant hepatic failure after acute hepatitis C is rare ***(CDC, 1998).***

Most (average: 94%) hemodialysis patients with newly acquired HCV infection have elevated serum ALT levels ***(Le Pogam et al., 1998).*** Elevations in serum ALT levels often precede anti-HCV seroconversion. Among prospectively followed transfusion recipients who developed acute HCV infection, elevated ALT levels preceded anti-HCV seroconversion (as measured by second generation assays) in 59%, and anti-HCV was detectable in most patients (78%) within 5 weeks after their first ALT elevation ***(Alter et al., 1991).***

After acute HCV infection, 15%-25% of persons with normal immune status appear to resolve their infection without sequelae as defined by sustained absence of HCV RNA in serum and normalization of ALT**.** In some persons, ALT levels normalized, suggesting full recovery, but this is frequently followed by ALT elevations that indicate progression to chronic disease ***(Alter and Seeff, 2000).***