INTRODUCTION

Hepatitis C virus (HCV) infection, first identified in ١٩٨٩, is caused by a blood-borne virus and affects an estimated ١٢٠ million individuals worldwide. Almost ٧٥٪ of HCV infections become chronic ***(Zuure et al., ٢٠١٠).***

This virus is efficiently transmitted by the parenteral route. As a consequence, people sharing needles and syringes, or submitted to blood transfusion and frequent vascular puncture are under increased risk of infection with HCV ***(Santos and Souto, ٢٠٠٧).***

The prevalence of anti-HCV antibodies in serum among hemodialysis (HD) patients is consistently higher than in the general population, indicating an increased risk of acquiring HCV infection among HD patients ***(Jasuja et al., ٢٠٠٩).***

The transmission of acute HCV among patients on maintenance HD is supported by various observations: An independent association between time on HD and HCV seroprevalence, the relationship between prevalence and incidence of anti-HCV in individual HD units, a higher frequency of anti-HCV seropositivity in patients on HD at a hemodialysis center compared with patients on peritoneal dialysis and home-HD treatment, and the relative homogeneity of HCV isolates in patients receiving treatment in the same HD unit. The small but definite incidence of acute HCV infection

detected in chronic HD patients, after the elimination of post-transfusion HCV, also confirms nosocomial HCV transmission ***(Martin and Fabrizi, ٢٠٠٨).***

When anti-HCV testing became available, it was observed that the prevalence of HCV in patients on dialysis varied greatly by geographic area (between ٤٪ and ٥٩٪ in different countries) ***(Prati, ٢٠٠٦).*** In Egypt, a recent study reported this prevalence to be as high as ٧٥٪ ***(Ibrahim, ٢٠١٠).*** The reported incidence depends upon the type of assay used, and execution trends for HD. Currently, third-generation anti-HCV ELISA is largely in use and has shown greater sensitivity and specificity in patients receiving HD ***(Jasuja et al., ٢٠٠٩).***

The estimated annual probability of a dialysis patient acquiring HCV depends on the characteristics of the center ***(Laporte et al., ٢٠٠٩).*** The factors that were constantly reported as being associated with an increased prevalence of HCV infection were the length of time on dialysis and the number of blood transfusions ***(Prati, ٢٠٠٦).***

Screening and careful attention to infection control precautions are mandatory for dialysis units to prevent the spread of hepatitis C. Prevention of spread is particularly important in these patients because HCV infection is associated with significant worsening of survival on dialysis therapy ***(Meyers et al., ٢٠٠٣).***

AIM OF THE STUDY

This study aims to estimate the incidence of seroconversion among HCV-negative patients undergoing regular hemodialysis at the Damanhour Fever Hospital in El-Beheira governorate. We further aim to assess the application of infection control practices (as recommended by the Egyptian Ministry of Health), and to evaluate HCV surveillance activities at this unit.

Chapter (١)

HEPATITIS C VIRUS

The World Health Organization (WHO) has declared hepatitis C a global health problem, with approximately ٣٪ of the world's population (roughly ١٧٠-٢٠٠ million people) infected with HCV ***(Mezban and Wakil, ٢٠٠٦)***. Of those infected, a reported ٨٠٪ fail to clear the virus, a significant number of whom will go on to develop severe liver disease, including cirrhosis and hepatocellular carcinoma (HCC) ***(Tran, ٢٠٠٨)***.

Hepatitis C is not known to cause disease in other animals. No vaccine against hepatitis C is currently available. The existence of hepatitis C (originally "non-A non-B hepatitis") was postulated in the ١٩٧٠s and proven in ١٩٨٩ ***(Houghton, ٢٠٠٩)***.

Infection with HCV results in a gamut of clinical outcomes ranging from viral elimination to the development of end-stage liver disease or HCC. Viral elimination, which occurs in a minority (~٢٠٪) of acutely HCV-infected individuals, is the result of effective immune control of HCV replication ***(Thio, ٢٠٠٨)***.

Genome organization:

Hepatitis C virus is a member of the Flaviviridae family. The genome consists of one single-stranded RNA molecule with positive polarity. It contains along translational open reading frame (ORF) that encodes a large viral polypeptide of ٣٠١١ amino acids.

ORF is translated to yield a polyphonies from which viral proteins derived by post-translational cleavage to yield structural (core and envelope) and non structural (ns) proteins (Fig. ١) ***(Lauer and Walker, ٢٠٠١)***.

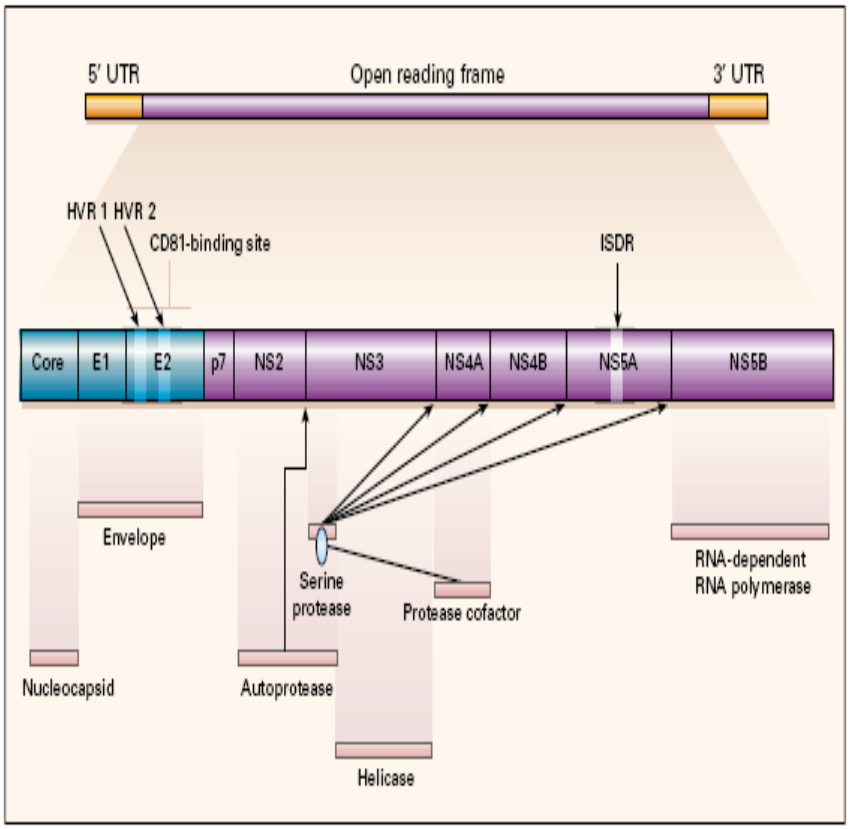

Fig. (١): Genetic structure of HCV ***(Lauer & Walker ٢٠٠١).***

The genome contains highly conserved untranslated regions (UTR) at both ٥' and ٣' termini, that are not translated into proteins but are important to translation and replication of the viral RNA. The structural region contains the nucleocapsid core protein and two envelope proteins that are located in the N-terminal quarter

while the non-structural protein is in the remaining portion of the polyphonies ***(Lauer and Walker, ٢٠٠١).***

This large pre-protein is later cut by cellular and viral proteases into the ١٠ smaller proteins that allow viral replication within the host cell, or assemble into the mature viral particles. Structural proteins made by the hepatitis C virus include Core protein, E١ and E٢; nonstructural proteins include NS٢, NS٣, NS٤, NS٤A, NS٤B, NS٥, NS٥A, and NS٥B ***(Dubuisson, ٢٠٠٧)***.

Genotypes:

There is increasing evidence that patients infected with different HCV genotypes have different clinical profiles, severity of liver disease and response to alpha-interferon therapy. Hence, a convenient and reliable HCV genotyping system is essential for large-scale epidemiological and clinical studies ***(Franciscus, ٢٠٠٧)***.

Six major genotypes of HCV have been defined. More than ٥٠ subtypes have also been described; the most common subtypes are ١a, ١b, ٢a, and ٢b. The evolution of genotypes has probably been influenced by several factors, including immune selection, infection patterns, replication efficiency, and population migration. So, there is a distinct geographic distribution of HCV genotypes:

Genotypes ١ are the most common seen in Europe and United state. Genotypes ٢ is present mostly in China, Japan and Western Europe. Genotypes ٣ in Scotland and Southern Italy, this genotype with genotype ٢ have the best response to interferon

therapy. Genotype ٤ is principally found in the Middle East, Egypt, this type is associated with a less response to interferon therapy than genotypes ٢،٣ and better than genotype ١. Type ٥ is almost exclusively found in Thailand, and genotypes ٦ is reported in Hong Kong ***(Chopra, ٢٠٠٩)***.

Each of the six main genotypes of HCV is equally divergent from one another and varies by as much as ٣٥٪ of nucleic acid content, while subtypes within a typical genotype differing from each other by ٢٠-٢٣٪. Within the infected host the viral pool comprises several different but closely related sequences called quasispecies, these may show up to ١٠٪ diversity ***(Omran et al., ٢٠٠٩).***

Epidemiology:

It is estimated that approximately ١٧٠-٢٠٠ million people worldwide are infected with hepatitis C virus (HCV) i.e., the prevalence of infection is nearly٣٪. According to data from WHO community and blood donor surveys ***(Mezban and Wakil, ٢٠٠٦).*** Most of whom are chronically infected. HCV-infected people serve as a reservoir for transmission to others and are at risk for developing chronic liver disease, cirrhosis, and primary hepatocellular carcinoma (HCC). It has been estimated that HCV accounts for ٢٧٪ of cirrhosis and ٢٥٪ of HCC worldwide. HCV infection has likely been endemic in many populations for centuries. However, the wave of increased HCV-related morbidity and mortality that we are now facing is the result of an

unprecedented increase in the spread of HCV during the ٢٠th century. Two ٢٠th century events appear to be responsible for this increase; the widespread availability of injectable therapies and the illicit use of injectable drugs ***(Alter, ٢٠٠٧).***

It is difficult to determine the number of new HCV infections, as most acute cases will not be noticed clinically. Fewer than ٢٥٪ of acute cases of hepatitis C are clinically apparent. In addition, the age of infection upon diagnosis is not possible to determine in most cases ***(Wasmuth, ٢٠٠٩).***

Epidemiology of HCV in Egypt:

In ١٩٩٢, when HCV antibody testing became widely available, the prevalence of HCV in Egypt was reported to be ١٠.٨٪ among first-time blood donors ***(Kamel et al., ١٩٩٢).*** Egyptian Demographic Health Survey (EDHS) in ٢٠٠٩ was a national probability sample of the resident Egyptian population.This report estimated an overall anti-HCV antibody prevalence of ١٤,٧٪ ***(El-Zanaty et al., ٢٠٠٩).***

Genotype ٤ represents over ٩٠٪ of cases in Egypt. Chronic HCV is the main cause of liver cirrhosis and liver cancer in Egypt and, indeed, one of the top five leading causes of death. In Egypt, the major route of exposure appears to be due to injection therapy and inadequate infection control practices. In addition to blood transfusions prior to ١٩٩٤, the major risk factor associated with HCV infection is a history of antischistosomal injection treatment

before ١٩٨٦. Prior to ١٩٨٦ the mainstay of treatment was intravenous tartar emetic. Widespread treatment campaigns were carried out in the countryside of Egypt in the ٦٠'s- ٧٠'s and early ٨٠'s. At the time of availability of only glass syringes, needles were routinely inadequately sterilized by boiling due to time restraints and limited resources***(Mezban and Wakil, ٢٠٠٦***).

Overall, despite improvement in schistosomiasis-related morbidity between ١٩٨٠- ١٩٩٠, these treatment campaigns set the stage for the current large hepatitis disease burden in Egypt. Further, with such a high background prevalence rate, transmission of hepatitis C through other non medical routes has become more significant. For example, tattooing, circumcision or other medical procedures performed by non-medical personnel are more frequent routes of infection in Egypt than elsewhere ***(Mezban and Wakil, ٢٠٠٦).***

Modes of transmission

HCV can be transmitted through various routes, like blood transfusion, recycling and reuse of syringes, unnecessary and unsafe injections, use of multi dose vial injection, organ transplantation, tattooing, body piercing, prenatal transmission, sexual exposure, house hold contacts, contaminated instruments i.e. endoscopes, traditional medicine, ear and nose piercing and sharing razors, particularly in rural areas ***(Alter, ١٩٩٥).***

The following are the currently known modes of transmission:

١) Iatrogenic medical or dental exposure:

People can be exposed to HCV via inadequately or improperly sterilized medical or dental equipment. Equipment that may harbor contaminated blood if improperly sterilized includes needles or syringes, hemodialysis equipment, oral hygiene instruments, jet air guns, etc. Limitations in the implementation and enforcement of stringent standard precautions in public and private medical and dental facilities is known to be the primary cause of the spread of HCV in Egypt, the country with highest rate of infection in the world ***(Miller and Abu- Raddad, ٢٠١٠).***

٢) Blood products:

Blood transfusion, blood products, or organ transplantation prior to implementation of HCV screening are all risk factors for hepatitis C virus transmission. Those who received blood or blood products as clotting factors, platelets, and plasma prior to the implementation of screening the blood supply for HCV may have been exposed to the virus ***(Choo et al., ١٩٨٩).***

٣) Injection drug use:

The prevalence of HCV infection in injection drug users ranges from ٥٧٪ to ٩٠٪ **(*Armstrong et al., ٢٠٠٦*)**. Injection drug use has always been the major route of HCV acquisition in the

United States and accounts for an increasingly large portion of cases, at least ٦٨٪ of new cases of HCV infection **(*Wasley et al.*, ٢٠٠٦).**

٤) Body piercings and tattooing:

Tattooing dyes, ink pots, stylets, and piercing implements can transmit HCV-infected blood from one person to another if proper sterilization techniques are not followed. Tattoos or piercings performed either before the mid ١٩٨٠s, "underground," or nonprofessionally are of particular concern, since sterile techniques in such settings may have been insufficient to prevent disease; sharing unsterilized tattooing equipment (for example, in the prison system) has an obvious increased risk of acquiring HCV ***(Vescio et al., ٢٠٠٨).***

The CDC states that, "Whenever tattoos or body piercing are performed in informal settings or with nonsterile instruments, transmission of hepatitis C and other infectious diseases is possible." ***(Vescio et al., ٢٠٠٨).***

٥) Shared personal care items:

Personal care items such as razors, toothbrushes, cuticle scissors, and other manicuring or pedicuring equipment can easily be contaminated with blood. Sharing such items can potentially lead to exposure to HCV *(**Lock et al.**, ٢٠٠٦).*

٦) Vertical transmission:

Vertical transmission refers to the transmission of a communicable disease from an infected mother to her child during the birth process. Mother-to-child transmission of hepatitis C has been well described, but occurs relatively infrequently ***(Mast, ٢٠٠٤).***

Transmission occurs only among women who are HCV RNA positive at the time of delivery; the risk of transmission in this setting is approximately ٦ out of ١٠٠. Among women who are both HCV and HIV positive at the time of delivery, the risk of transmitting HCV is increased to approximately ٢٥ out of ١٠٠.The risk of vertical transmission of HCV does not appear to be associated with method of delivery or breastfeeding ***(Mast, ٢٠٠٤).***

٧) Sexual exposure:

Sexual activities and practices were initially identified as potential sources of exposure to the hepatitis C virus. More recent studies question this route of transmission ***(Tohme and Holmberg, ٢٠١٠)***.

Sexual transmission of HCV is considered to be rare. Studies show the risk of sexual transmission in heterosexual, monogamous relationships is extremely rare or even nil ***(Vandelli et al., ٢٠٠٤).***

The CDC does not recommend the use of condoms between long-term monogamous discordant couples (where one partner is

positive and the other is negative). However, because of the high prevalence of hepatitis C, this small risk may translate into a nontrivial number of cases transmitted by sexual routes. Vaginal penetrative sex is believed to have a lower risk of transmission than sexual practices that involve higher levels of trauma to anogenital mucosa ***(Hahn, ٢٠٠٧).***

High risk groups for HCV infection:

A- Poly-transfused patients: (Thalassemic patients, Leukemic patients and Patient with renal dialysis) ***(Fissell et al., ٢٠٠٤).*** Persons with hemophilia should be tested for HCV infection if blood products were received before ١٩٨٧, after which time, viral inactivation procedures were implemented ***(Goedert et al., ٢٠٠٧).***

B- Intravenous drug abusers: because of sharing syringes and other blood contaminated equipments, HCV is wide spread among parenteral drug consumers ***(Alter, ٢٠٠٦).***

C- Needle stick exposure: Risk group includes professionals occupationally exposed to blood or its products such as surgeons, dentists, pathologists and laboratory technicians. Studies showed that approximately ١٠٪ of infected needle stick accident result in virus transmission ***(Datta et al., ٢٠٠٣).***

D- Health care workers : Medical and dental personnel can be exposed to HCV through accidental exposure to blood through needle sticks or blood spatter to the eyes or open wounds. Universal precautions to protect against such accidental

exposures significantly reduce the risk of exposure to HCV ***(Vandelli et al., ٢٠٠٤).***

E- Hemodialysis patients: Chronic hemodialysis patients are at high risk for infection because the process of hemodialysis requires vascular access for prolonged periods. In an environment where multiple patients receive dialysis concurrently, repeated opportunities exist for person-to-person transmission of infectious agents, directly or indirectly via contaminated devices, equipment and supplies, environmental surfaces, or hands of personnel. Furthermore, hemodialysis patients require frequent hospitalizations and surgery, which increases their opportunities for exposure to nosocomial infections ***(CDC, ٢٠٠١).***

Clinical manifestation and sequales of HCV:

- **Acute hepatitis**

Patients who sustain acute HCV infections are typically asymptomatic. Only٢٠٪ of them become clinically jaundiced. The primary HCV infection is poorly characterized, and most of the clinical picture of acute hepatitis C has mainly come from post transfusion infection. Transition from acute to chronic hepatitis and evolution to cirrhosis almost always occurs in the absence of symptoms ***(Seeff, ٢٠٠٢).***

The symptomatic onset of acute HCV infection varies between cases with a range of ٣-١٢ weeks after exposure.Acute

hepatitis C can be severe and prolonged but is rarely fulminant ***(Hoofnagle, ٢٠٠٢).***

- **Chronic hepatitis**

At least ٨٥٪ of individuals acutely infected with HCV develop chronic HCV infection ***(Cheney et al., ٢٠٠٠).***

Chronic infection with hepatitis C virus (HCV) is the leading cause of cirrhosis and the most common indication for liver transplantation in many countries throughout the world. The most significant factors leading to cirrhosis progression in patients with chronic HCV infection include the degree of inflammation present on liver biopsy and ongoing alcohol use ***(Shiffman, ٢٠٠٣).***

- **Clinical Features of Cirrhosis**

Cirrhosis is the final irreversible stage of chronic hepatitis and/or cell injury. It is a diffuse process of fibrosis and nodule formation following hepatocellular necrosis ***(Sherlock and Dooley, ٢٠٠٢).***

Transforming growth factor (TGF)-beta plays a pivotal role in the pathogenesis of post-inflammatory liver scarring. HCV core protein expression may up regulate directly TGF-beta transcription in parenchymal cells and suggest a new paradigm for exacerbation of liver cirrhosis by HCV infection ***(Taniguchi et al., ٢٠٠٤).***

Once a patient develops cirrhosis, symptoms and signs are more prominent. In addition to fatigue, the patient may complain of