INTRODUCTION

Hepatitis C continues to be a major public health problem affecting approximately 3% of the global population. According to the World Health Organization, an estimated 170 million people have chronic hepatitis C. 10% to 20% of those who are chronically infected with hepatitis C will progress to cirrhosis and 5% will develop hepatocellular carcinoma ***(Mindikoglu and Ram, 2009).***

Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis and hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are anti-HCV positive. The strong homogeneity of HCV subtypes found in Egypt (mostly 4a) suggests an epidemic spread of HCV ***(WHO, 2002).***

Hepatitis C is the most common liver disease in renal dialysis patients while liver disease itself is a significant cause of morbidity and mortality in patients with end-stage renal disease (ESRD) treated by dialysis or transplantation ***(Rahnavardi et al., 2008).***

A number of risk factors identified for HCV infection among dialysis patients, which number of blood transfusions, duration of end stage renal diseases, mode of dialysis and concurrent prevalence of HCV infection the dialysis unit ***(Jasuja et al., 2009).***

The most likely cause of HCV transmission between patients treated in the same dialysis unit is cross-contamination from supplies and surface (including gloves) as a result of failure to follow infection-control procedures within the unit. Other possible transmission routes are direct contact between patients, a common infected blood donor, or invasive procedures outside using contaminated instruments ***(Fabrizi and Martin, 2010).***

There is a wide variation in the prevalence of HCV infection among different dialysis units and countries as shown by Dialysis Outcomes and Practice Patterns Study (DOPPS). Mean HCV facility prevalence was 13.5% and varies among countries from 2.5-22.9% ***(Fissell et al., 2004).***

In Egypt, the prevalence of HCV infection was variable ranging from 49% to 64% ***(Egyptian renal registry, 2008 report).***

The Center for Disease Control and Prevention (CDC) does not currently recommend designated machines or patient isolation to prevent transmission of HCV within HD units ***(CDC, 2001).***

Similar recommendations were expressed in the recently published Kidney Disease Improving Global Outcomes statements ***(KDIGO guidelines, 2008).***

Some prospective trials have shown a reduction in HCV transmission within dialysis units by complete isolation of anti–HCV-seropositive patients ***(Gallego et al., 2006)***. It remains unclear whether the reported improvement resulted from adoption of an isolation policy or rather from the simultaneous reinforcement of the application of infection control procedures ***(Fabrizi and Martin, 2010).***

Diagnostic tests used for the detection of HCV infection include the HCV antibody enzyme immunoassay (EIA), recombinant immunoblot assay (RIBA), and HCV RNA polymerase chain reaction (PCR) ***(Ghany et al., 2009).***

The most widely used initial assay for detecting HCV antibodies is the EIA. A positive EIA should be followed by a confirmatory test. When used in low-risk groups, an EIA may yield false positive results. RIBA, a confirmatory test for a positive EIA, detects antibodies to individual HCV antigens and has a greater specificity ***(Wilkins et al., 2010).***

The detection of HCV RNA by PCR has been used as the "gold standard" to identify current HCV infection ***(Fabrizi et al., 2008)***. There are two types of PCR assays presently available – qualitative and quantitative. The qualitative PCR assays are considered the most sensitive tests for the diagnosis of HCV infection ***(Podzorski, 2002).***

Although more than 90% of non-immunosuppressed individuals with HCV infection test positive for anti-HCV, some patients are anti-HCV negative despite being positive for HCV RNA. Possible explanations for this result include various diseases, conditions, or pharmacologic immuno-suppression could suppress or modify the anti-HCV response ***(Fabrizi et al., 2008).***

AIM OF THE WORK

To determine the incidence of HCV seroconversion among patients undergoing hemodialysis in two units adopting different isolation policies both of which follows the same standard precautions and verifying the role of such isolation and other risk factors in virus seroconversion if any.

HEPATITIS C VIRUS

Epidemiology

It is estimated that over 170 million people worldwide are infected with hepatitis C virus (HCV), and although the rate of new infections is rapidly declining, the prevalence of HCV infection is not predicted to decrease in the near future ***(Tester et al., 2005).***

The global scale of HCV is not well known, owing to the asymptomatic nature of the acute phase of infection. However, it is accepted that approximately 2-4 million individuals are chronically infected in the United States, 5-10 million in Europe, and upwards of 12 million in India. Especially alarming are numerous Middle Eastern and African countries such as Egypt, with HCV prevalence ranging anywhere from 1-12% of the entire population ***(Timm et al., 2004).***

In fact, HCV has been found in every part of the world where it has been sought, highlighting the virus' successful transmission and persistence in the human population. HCV causes persistent infection in approximately 70% of all documented cases, and can lead to liver failure, portal hypertension, and hepatocellular carcinoma ***(Thimme et al., 2001).***

The virus is transmitted percutaneously or permucosally. Blood products, hemodialysis, and solid organ transplantation

were the main routes of transmission.The incubation period of HCV, though ranging up to several months, averages 6-8 wk. HCV infection is often asymptomatic, making it a very difficult to detect it at an early stage ***(Dazert et al., 2009).***

This is the major reason why early treatment is difficult. Therefore, hepatitis C is often referred to as a "silent disease". In a majority of infected people, virus infection does not resolve naturally. Neutralizing antibodies appear to be produced during the course of a natural infection, yet the virus mutates to escape surveillance ***(Von Hahn et al., 2007).***

When liver fails to clear the virus, the individuals become chronic carriers. However, within this chronically infected population the disease outcomes vary, it can be mild (minimal inflammation of the liver) or severe and can lead to scar tissue formation.

Chronic infection with HCV is a major risk factor for cirrhosis, a disease associated with significant morbidity and mortality ***(Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients annual registry, 2011).***

Complications of cirrhosis include portal hypertension, ascites, hepatic encephalopathy, esophageal varices, and hepatocellular carcinoma (HCC) ***(Bruno et al., 2009).*** The natural history of HCV infection is summarized in figure (1).

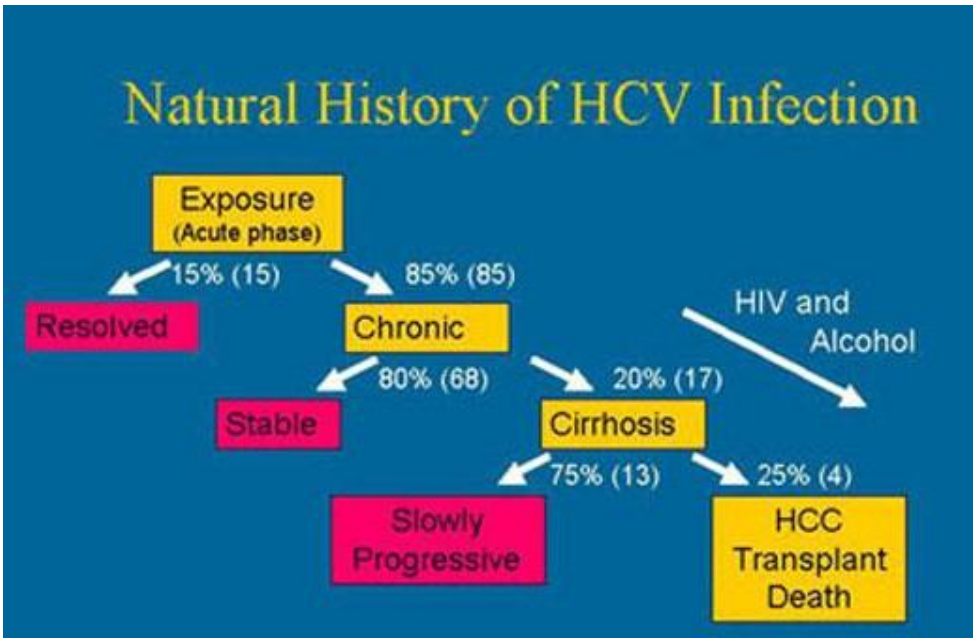

Figure (1): Natural History of HCV infection.

Clearly, HCV has taken and will continue to extract a toll on the human species until successful treatment and eradication protocols can be established.

Molecular Biology of HCV

HCV is an enveloped single-stranded RNA (ssRNA) virus that is both hepatotrophic and non-cytopathic, belonging to the genus Hepacivirus and the family Flaviviridae ***(Bukh et al., 1995).***

Virions typically have a short half-life of 3 hours, and viral loads between 103-107 genomes per ml of serum are common in most patients ***(Fuller et al., 2010).***

These factors combined with a highly error-prone RNA-dependent RNA replication mechanism have generated a remarkably diverse virus, with HCV being grouped into at least six major genotypes comprised of numerous subtypes that exist as a quasispecies swarm inside infected individuals ***(Puig et al., 2006).***

HCV particles are thought to be approximately 50 nm in diameter, based on limited imaging data and predictions using analogous flaviviruses ***(Urbani et al., 2006).***

The HCV nucleocapsid is composed of copies of the core protein studded with heterodimer pairs of the E1 and E2 glycoproteins, all of which encapsidate the RNA genome (figure 2) ***(Smyk-Pearson et al., 2008).***

Interestingly, plasma-derived HCV has been shown to associate with both low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) and infectivity of particles may be enhanced as a result ***(Day et al., 2003).***

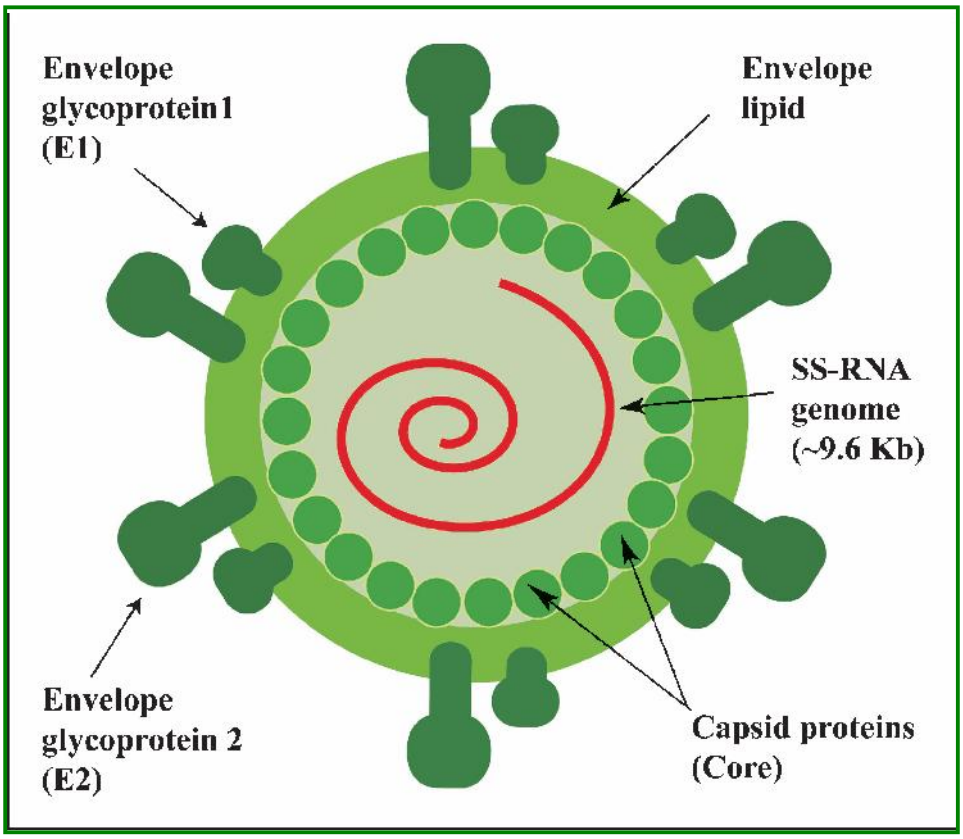

Figure (2): Hepatitis C virus particle structure.

Viral Life Cycle

In general, the infectious life cycle of an HCV virion can be broken down into the following stages:

I. <u>Binding and Entry</u>:

Virus binding and entry occurs in a permissive cell, typically a hepatocyte. This process is mediated by specific

molecules on both the cell and virion, and most likely occurs in a stepwise manner. We will devote a comprehensive review to the description of this process, as it pertains directly to work contained herein.

II. Fusion and Uncoating:

The lipid bilayer of the virion fuseswith the host endosomal membrane, releasing the positive-sense ssRNA genome into the cytoplasm of the cell. Although this process is not well understood, it is known that a low pH-triggering event is necessary for this step to occur, and a recent publication has postulated that motifs in viral surface molecules may adopt specific conformations to aid in fusion ***(Scarselli et al., 2002).***

III. Virion Maturation and Egress:

The newly released genome undergoes direct translation at the endoplasmic reticulum and potentially other membranes, as well as replication through a negative-strand intermediate, followed by packaging into a finished virion assembled from the processed viral proteins. Finally, mature virions bud from the endoplasmic reticulum or associated membranes, and are released from the host cell through traditional secretory pathways to begin the process a new.

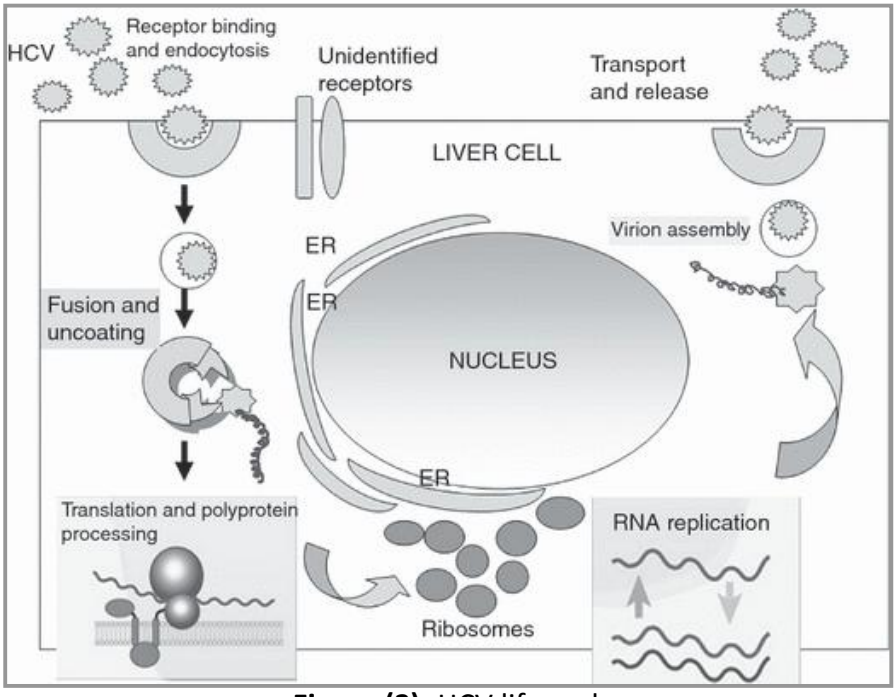

Figure (3): HCV life cycle.

Infectivity

Although HCV can be widely disseminated in many organs and tissues, it is generally believed that itsability of cell entry and replication is limited to the hepatocytes and B-lymphocytes. Sporadic reports suggest that replication may also occur in other sites such as the circulating dendritic cells ***(Goutagny et al., 2003)*** and the renal tubules ***(Kasuno et al., 2003)***.

For the establishment of a successful life cycle in the target cells, the virus must get attached to its surface, break

through the cell membrane, expose its genome, multiply, synthesize its non-structural proteins, acquire a new envelope and leave the cell to infect another ***(Cocquerel et al., 2006).***

Glycosaminoglycans and lectins are mainly involved in the initial, low-affinity attachment of the virus to many cells. Low-density lipoprotein and asialoglycoprotein receptors subsequently induce viral endocytosis, which is a common mechanism for cell entry of all flaviviridae. While within the endocytic vesicle, the virus is exposed to a relatively low pH, which induces a conformational change that adapts it to attach to high-affinity receptors on the cell membrane ***(Bartosch et al., 2006).***

The best known of these are CD81 and the scavenger receptor B1 (SR-B1), the combination of which seems essential for the release of HCV into the cytoplasm. CD81 is a member of the tetraspanin superfamily (hence the synonym TAPA-1), which encompasses a large number of proteins with four transmembrane domains and are able to integrate with each other and with other membrane proteins to form specific receptors. SR-B1 is a glycoprotein on human scavenger cells, which has two N-terminal cytoplasmic domains separated by a large exracellular domain, involved in apoptosis and lipid uptake ***(Cocquerel et al., 2006).***

While CD81 may be independently involved in the initial viral attachment to the cells, its integration with SR-B1 seems

crucial for firm attachment with the E2 envelop glycoproteins, leading to a critical configurational change essential for viral fusion and subsequent intracellular release. Either CD81 or SR-B1 may be present on many cell membranes, yet their co-existence, as on the hepatocytes, is essential for permissiveness to HCV entry. The involvement of other membrane proteins is suggested by the co-existence of CD81 and SR-B1 in non-permissive cells ***(Cocquerel et al., 2006).***

Upon successful intracellular release of the virus, it interacts with several host proteins in a poorly understood manner. One of the interesting interactions occurs between NS5B and cyclophyllin B, which increases its polymerase binding affinity to viral RNA, a process that can be inhibited by cyclosporine, hence its antiviral activity ***(Ma et al., 2006).***

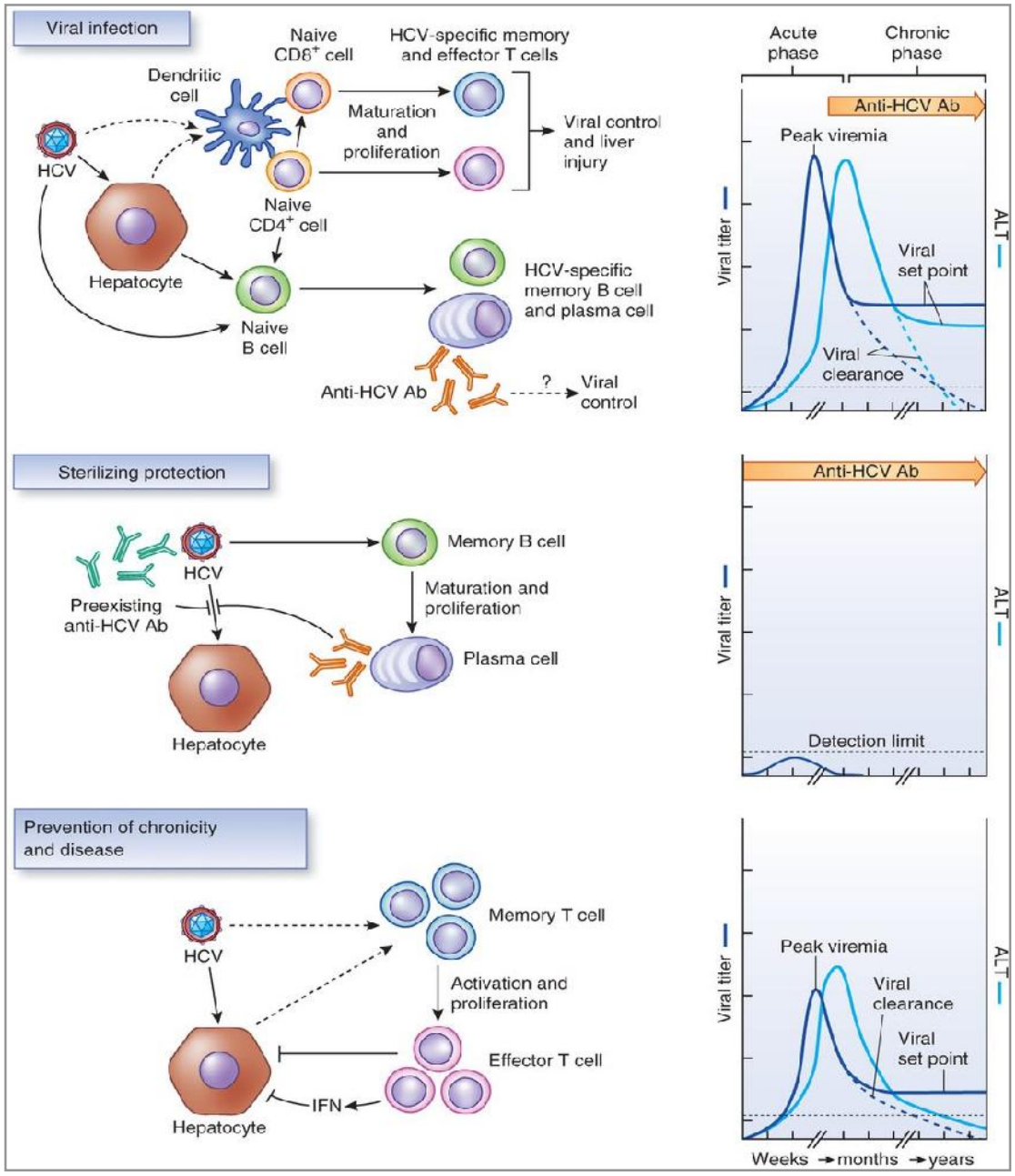

Figure (4): HCV infectivity process.