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Review Article

A REVIEW ON HEPATITIS AND HAEMOSTASIS

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Abstract

Hepatitis is a medical condition which is defined by the inflammation of the liver and characterized by the presence of inflammatory cells in the tissue of the organ which can be self-limiting or progress to fibrosis and cirrhosis. Inflammation of the liver can be viral or non-viral. It is called viral when viruses are associated with the inflammation e.g. Hepatitis A virus, Hepatitis B virus and Hepatitis C virus. It is called non Viral when other factors are involved via; alcohol, organic solvents, infections, autoimmune diseases, drugs toxins etc. This is a collection of complex interrelated systemic mechanisms operating to maintain balance between coagulation and anticoagulation. It is a process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system. Most coagulation factors and inhibitors of the coagulation and fibrinolytic system are markedly reduced in liver cirrhosis because of impaired protein synthesis, except for factor VIII and fibrinogen levels, which may be normal or increased. Possible explanations for the increased factor VIII levels are the increased hepatic biosynthesis of vWF and decreased expression of low-density lipoprotein receptor –related protein, both of which modulate the levels of factor VIII in plasma, rather than increased factor VIII synthesis. The deficiency of vitamin K-dependent factors in cirrhosis may occur by several mechanisms, including reduced hepatic synthesis and reduced absorption of Bile salts required for absorption of vitamin K-dependent factors, which may occur in setting of cholestatic liver diseases. Other contributing factors include poor oral intake and treatment with antibiotics that destroy the intestinal bacterial that synthesis vitamin K. As with acute liver diseases, the reduction in coagulation factors parallel the degree of progression of liver diseases

Keywords: Hepatitis, fibrosis and cirrhosis, coagulation and fibrinolytic system, biosynthesis of vWF.

Introduction

HEPATITIS

The liver is the largest gland in the body with many complex functions. These include among other things, the synthesis of acute phase proteins, transport proteins and clothing factors (William, 2003). But when this organ is diseased as a result of viral or non viral factors, there is a malfunction due to inflammation (Hepatitis) and consequent death of the organ.

Hepatitis is a medical condition which is defined by the inflammation of the liver and characterized by the presence of inflammatory cells in the tissue of the organ which can be self-limiting or progress to fibrosis and cirrhosis (Ryder and Beckingham, 2001).

Hepatitis may be assymptomatic or symptomatic but often, leads to jaundice, anorexia and malaise. It can be caused by viruses (including hepatitis viruses A, B and C) and non-viruses (alcohol, certain medications, some organic solvents and plants, infections, and autoimmune diseases) ; can be acute – lasting for less than six months or chronic – persisting for longer period of time (Ryder and Beckingham, 2001).

CLASSIFICATION OF HEPATITIS

Hepatitis can be classified as being acute when it lasts less than six months and chronic when it persists for a longer period of time.

A. Acute hepatitis: In acute hepatitis, the lesions predominantly contain diffuse sinusoidal and portal mononuclear infiltrates (lymphocytes, plasma cells, kupffer cells) and swollen hepatocytes. Acidophilic cells (Coumcilman bodies) are common. Heptatocyte regeneration and cholestasis typically are present. Bridging hepatic necrosis may also occur with some lobular disarray (Gimson, 1996). Although aggregates of lymphocytes in portal zone may occur, these are usually neither common nor prominent. There is no evidence of fibrosis or cirrhosis in acute hepatitis. However, in severe cases, prominent hepatocellular necrosis around the central zone may be seen (Gimson, 1996).

In submissive necrosis – a rare presentation of acute hepatitis – there is widespread hepatocellular necrosis beginning in the centrizonal distribution and progressing towards portal tracts. The degree of parenchymal inflammation is variable and is proportional to duration of disease (Kirsch et al., 2009).

There are two district patterns of necrosis that have been recognized: zonal coagulative necrosis and panlobular (non zonal) necrosis (Kirsh et al., 2009). Necrosis and inflammation of the biliary tree occur with hyperplasia of the surviving biliary tract cells. (Nakanuma et al., 1994). Stromal haemorrhage is also common.

B. **Chronic Hepatitis:** Chronic hepatitis can be with or without piecemeal. It is called a chronic necrosis with piece meal (periportal) when it is occurring for more than six months with portal based inflammation, fibrosis, disruption of the terminal plate, and piecemeal necrosis.

It is without piecemeal necrosis when there is no significant periportal necrosis or regeneration with a fairly dense mononuclear portal infiltrate. Councilman bodies are frequently seen within the lobule (Wanless, 1995).

Cirrhosis is a diffuse process characterized by regenerative nodules that are separated from one another by bands of fibrosis. It is the end stage for many chronic liver diseases. The patho-physiological process that result in cirrhosis is as follows: Hepatocytes are lost through a gradual process of hepathocellular injury and inflammation. This injury stimulates a regenerative response in the remaining hepatocytes. The fibrotic scars limit the extent to which the normal architecture can be reestablished as the scars isolate groups of hepatocytes. This results in nodules formation. Angiogenesis (New Vessel Formation) accompanies scar production which results in the

formation of abnormal channels between the central hepatic veins and the portal vessels. This in-turn causes shunting of blood around the regenerating parenchyma. Normal vascular structures including the sinusoidal channels may be obliterated by fibrotic tissue leading to portal hypertension. The overall reduction in heptatocyte mass, in conjunction with the portal blood shunting, prevents the liver from accomplishing its usual functions (Selves et al., 2010).

TYPES OF HEPATITIS

Inflammation of the liver can be viral or non-viral. It is called viral when viruses are associated with the inflammation e.g. Hepatitis A virus, Hepatitis B virus and Hepatitis C virus. It is called non Viral when other factors are involved via; alcohol, organic solvents, infections, autoimmune diseases, drugs toxins etc.

Non Viral Hepatitis

This is a type of liver inflammation caused by factors other than viruses. There are;

A. **Alcoholic hepatitis:** Alcoholic hepatitis which comes after a period of increased alcohol consumption is characterized by a variable constellation of symptoms, which may include feeling unwell, enlargement of the liver development of fluid in the abdomen ascites, and modest elevation of liver blood parameters. Alcoholic hepatitis can vary from mild with only liver test elevation to severe liver inflammation with development of jaundice, prolonged prothrombin time, and liver failure (Connor and Schwartz, 2005). Severe cases are characterized by either obtundation (dulled consciousness) or the combination of elevated bilirubin levels and prolonged prothrombin time.

Alcoholic hepatitis is distinct from cirrhosis caused by long-term alcohol consumption as alcoholic hepatitis does not lead to cirrhosis, but cirrhosis is more common in patients with long-term alcohol consumption. And it has been shown that the combination of hepatitis C and alcoholc consumption accelerates the development of cirrhosis (Connor and Schwartz, 2005).

B. **Drug – Induced Hepatitis:** Human variability is such that any drug can be a cause of hepatitis. The clinical course of drug-induced hepatitis is quite variable depending on the drug and the patient's tendency to react to the drug. For example halothane hepatitis can range from mild to fatal as can Isoniazid (Lim et al., 2006). Hormonal contraception can cause structural changes in the liver. Amiodaron hepatitis can be untreatable since the long half life of the drug (up to 60 days), means that there is no effective way to stop exposure to the drug (Lim et al., 2006). Statins can cause elevations of liver function blood tests parameters normally without indicating an underlying hepatitis.

C. Toxins: A portion of a single Amatoxin – containing mushrooms such as Death cap (Amanita phalloides), Destroying Angel (Amanita Ocreata) and some species of Galerina can be enough to be lethal (10mg or less of α - amanitin) (Lim et al., 2006). Others include white phosphorous – an industrial toxin and war chemical, carbon tetrachloride, chloroform and trichloroethylene – which can cause steatohepatitis. Another toxin is the cylindrospermopsin – a toxin from the cyanobacterium (cylindrospermopsisraciborskii).

D. Metabolic disorders: Some metabolic disorders can cause different forms of hepatitis. For example Hemochromatosis and Wilson's disease – diseases of iron and copper accumulations respectively, can cause liver inflammation and necrosis. Non-alcoholic steatohepatitis is effectively a consequence of metabolic syndrome (Nadiv et al., 2000).

E. Obstructive Disorders: Obstructive jaundice is a jaundice occurring due to obstruction of the bile duct (gallstone or external obstruction by cancer). If long standing, leads to destruction and inflammation of liver tissues.

F. Autoimune Disorders: Abnormal presentation of human Leukocyte antigen (HLA) Class II on the surface of heptacocytes, possibly due to genetic predisposition or acute liver infection, causes a cell-mediated immune response against the body's own liver, resulting in autoinmine hepatitis.

G. Alpha I - antitrypsin Deficiency: In severe cases of alpha I anti trypsin deficiency, the accumulated protein in the endoplasmic reticulum causes liver cell damage and inflammation.

H. Non – alcoholic Fatty liver Diseases: It is commonly associated with obesity and mostly in women. severe NAFLD Leads to inflammation, a state referred to as non-alcoholic steatohepatitis (NASH). NASH is becoming recognized as the most important cause of liver disease second only to hepatitis C in numbers of patients going on to cirrhosis (Connor and Schwartz, 2005).

I. Ischemic Hepatitis: This is caused by decreased circulations to the liver cells, usually due to decreased blood pressure (or shock), leading to the equivalent term "Shock liver". Ischemic hepatitis can be caused by localized problems within the blood vessels that supply oxygen to the liver (such as thrombosis, or clothing of the hepatic artery) (Hayashi et al., 2011).

J. Giant Cell Hepatitis: This is rare form of hepatitis that predominantly occurs in children. The Diagnosis is made on the basis of the presence of hepatocellular multinucleate giant cells ((Kirsch et al., 2009). Cases presenting in adults are rare and tend to be rapidly progressive (Hartl et al., 2010). The cause is currently unknown but an infectious cause is suspected. The condition tends to improve with the use of ribivirin, suggesting a viral origin suggestive of hepatitis E, hepatitis C, paramyxovirus, papillomavirus and Human herpes virus 6 (Moreno et al., 2006).

VIRAL HEPATITIS

This is the inflammation of the liver tissues brought about by viral infections. These viruses include among others, hepatitis A, B, and C viruses.

A. **Hepatitis A virus:** This was formerly known as infectious hepatitis and epidemical virus. It is an acute infectious disease of the liver caused by hepatitis A virus (Hep A) (Ryan and Ray, 2004). Hep A is an RNA virus usually spread by the facal-oral route; transmitted person to person by ingestion of contaminated food or through direct contact with an infectious person. The incubation period is between two and six weeks with an average period of 28 days (Connor, 2005).

- **Structure of Hep.A:** HAV belongs to the family of picornavirus and it's non-enveloped and contains a single-stranded RNA packaged in a protein shell (Cristina and Costa-Mattioli, 2007). There is only one serotype of the virus, but multiple genotypes exist. Codon use within the genome is biased and usually distinct from its host. It also has a poor internal ribosome entry site (Whetter et al., 1994). In the region that codes for the HAV capsid, there are highly conserved clusters of rare codon-s that restrict antigenic variability (Aragones et al., 2008).

- **Transmission**: HAV is spread by the fecal-oral route and infections often occur in conditions of poor sanitation and overcrowding. It can also be transmitted by the parenteral route but very rarely by blood and blood products. Food-borne outbreaks are not uncommon (Brundage and Fitzpatrick, 2006) and ingestion of shellfish cultivated in polluted water is associated with a high risk of infections. Approximately, 40% of all acute viral hepatitis is caused by HAV (Murray et al., 2005) and infected individual are infectious prior to onset of symptoms, roughly 10 days following infection (Murray et al., 2005). The virus is resistant to detergent, acid (PH I), solvents (ether, chloroform), drying, and temperatures up to 60^{o}c. It can survive for months

in fresh and salt waters. The infection is common in children but following infection there is life long immunity (Brundage and Fitzpatrick, 2006). Hepatitis A virus can be inactivated by chlorine, formulain (0.35%, 37^{o}c, 72 hours), peracetic acid (2%, 4 hours), beta – propidactone (0.25%, 1 hour), and UV radiation (24 Կw/cm^{2}/min) (Lees, 2000).

- **Pathogenesis**: Following ingestion of HAV, it enters the blood stream through the epithelium of the oropharynx or intestine (Murray et al., 2005). The virus is carried in the blood to the liver which is its target organ where it multiplies within hepatocyctes and kupffer cells. The virions are secreted into the bile and released in stool. HAV is excreted in large quantities approximately 11 days prior to appearance of symptoms or anti-HAV 1gM antibodies in the blood (Murray et al., 2005). The incubation period is 15-50 days and mortality is less than 0.5%. Within the liver hepatocytes, the RNA genome is released from the protein coat and is translated by the cell's own ribosomes. Unlike other members of the picornaviruses, HAV requires intact eukaryote initiating factor 4G (elF4G) for the initiation of translation (Aragones et al., 2010). The requirement for this factors results in an inability to shutdown host protein synthesis unlike other picornaviruses. The virus must then inefficiently compete for the cellular translational machinery which may explain its poor growth in cell culture (Aragones et al., 2010).

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-**Genotypes of HAV**: Only one genotype and seven different genetic groups (four humans and three simian) have been described (Cristina and Costa-Mattioli, 2007). The human genotypes are numbered I – III. Six subtypes have been described (IA, IB, IIA, IIB, IIIA, IIIB). The simian genotypes have been numbered IV-VI. A single isolate of genotype VII isolated from a human, has also been described (Cling et al., 2002). Genotype III has been isolated from both humans and owl monkeys. Most human isolates are of genotype I and of the type I isolates, -subtype IA accounts for the majority (De-Paula et al., 2002).

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-**Epidemiology of HAV**: In developing countries and in regions with poor hygiene standards, the incidence of infection with this virus is high and it is usually contracted in early childhood (Steffen, 2005). As income rises and access to clean water increases, the incidence of HAV decreases (Jacobsen and Koopman, 2005). In Europe, United States and other industrialized countries, the infection is contracted primarily by susceptible young adults unlike low-income regions (sub-saharan Africa and parts of South Asia) where there is no susceptible adolescents and adults due to high endemicity (Jacobsen and Wiersma, 2010). And most of these people from the industrialized regions contract it during their trips to countries with high endemicity or through contact with infectious person (Connor, 2005).

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-**Signs and Symptoms**: Early symptoms of hepatitis A infection can be mistaken for influenza, but some sufferers, especially children, exhibit no symptoms at all. Symptoms typically appear 2 to 6 weeks after the initial infection. Symptoms usually last less than 2 months, although some people can be ill for as long as 6 months. These include; fatigue, fever, abdominal pain, nausea, appetite loss, jaundice, clay-colouredfaecesetc (Connor, 2005).

B. Hepatitis B Virus (HBV): Hepatitis B virus is a member of the Hepadinavirus family with the virionsconstiting of an outer lipid envelope and an icosahedral nucleocapsid core composed of protein. These virions are 42nM in diameter and are sometimes referred to as "Dane particles" (Harrison, 2009). The nucleocapsid encloses the viral DNA ad a DNA polymerase that has reverse transcriptase activity (Locamini, 2004) and the outer envelope contains embedded proteins that are involved in viral binding of, and entry into, susceptible cells. The virus is one of the smallest enveloped animal viruses, but pleomorphic forms exist including filamentous and spherical bodies lacking a core. These particles are not infectious and are composed of

the lipid and protein that form part of the surface of the virions which is called the surface antigen (HBsAg) and is produced in excess during the life cycle of the virus (Howard, 1986). Hepatitis B virus infection on the other hand is an infectious inflammatory illness of the liver caused by the hepatitis B virus (HBV) that affects honiridea including humans. Originally it was known as "serum hepatitis". It has caused epidemics in parts of Asia and Africa, and it is endemic in China (Sleisenger et al, 2006). About a third of the world population has been infected at one point of their lives, including 350 million who are chronic carriers (Williams, 2006).

-**History:** The earliest record of an epidemic caused by hepatitis B virus was made by Lurman in 1885 (Lurman, 1885). An outbreak of small pox occurred in Bremen in 1883 and 1,289 shipyard employees were vaccinated with lymph from other people. After several weeks, and up to eight months later, 191 of the vaccinated workers became ill with jaundice and were diagnosed as suffering from serum hepatitis. Other employees who had been inoculated with different batches of lymph remained healthy. Lurman's paper, now regarded as a classical example of an epidemiological study, proved that contaminated lymph was the source of the outbreak. Later, numerous similar outbreaks were reported following the introduction, in 1909 of hypodermic needles that were used, and more importantly, reused, for administering salvascan for the treatment of syphilis. The virus was not discovered until 1965 when Baruch Blumberg, then working at the National Institute of Health (NIH), discovered the Australia antigen (Later known as hepatitis B surface antigen, or HBsAg) in the blood of Australian aboriginal people (Alter and Blumberg, 1966). Although a virus had been suspected since the research published by MacCallum in 1947 (MaCallum, 1947). Dane, D.S and others discovered the virus particle in 1970 by electron microscopy (Dane et al., 1970). By early 1980s the genome of the virus had been sequenced (Gilbert el al., 1979) and the first vaccines were being tested.

-**Genome of HBV:** The genome of HBV is made of circular DNA, but it is unusual because the DNA is not fully double – stranded. One end of the full length strand is linked to the viral DNA polymerase. The genome is 3020 – 3320 nucleotides long (for the full-length strand) and 1700 – 2800 nucleotides long (for the short length – strand) (Kay and Zoulim, 2007). The negative-sense, (non-coding), is complementary to the viral mRNA. The viral DNA is found in the nucleus soon after infection of the cell. The partially double-stranded DNA is rendered fully double-stranded by completion of the (+) sense strand and removal of a protein molecule from (-) sense strand and a short sequence of RNA from the (+) sense strand. Non-coding bases are removed from the ends of the (-) sense strand and the ends are rejoined. There are four known genes encoded by the genome, called C, X, P and S. The core protein is coded for by gene C (HBcAg), and its start codon is preceded by an upstream in – frame AUG start codon from which the pre-core protein is produced. HBeAg is produced by proteolytic processing of the pre-core protein. The DNA polymerase is encoded by gene P. Gene S is the gene that codes for the surface antigen (HBsAg). The HBsAg gene is one long open reading frame but contains three in frame "start" (ATG) Codons that divide the gene into three sections, pre – S1, Pre – S2 and S. Because of the Multiple start codons, polypetides of three different sizes called large, middle, and small (Pre-S1+Pre-S2+S, Pre – S2 + S, or S) are produced. The function of the protein coded for by gene X is not fully understood but it is associated with the development of liver cancer. It stimulates genes that promote cell growth and inactivates growth regulating molecules (Li et al., 2010).

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-**Replication of HBV:** HBV is one of the few known pararetroviruses: non-retroviruses that still use reverse transcription in their replication process. The virus gains entry into the cell by binding to an unknown receptor on the surface and being endocytosed in. Because the virus multiplies via RNA made by a host enzyme, the viral genomic DNA has to be transferred to the cell nucleus by host protein called charperones.

The partially double stranded viral DNA is then made fully double stranded and transformed into covalently closed circular DNA (CCC DNA) that serves as a template for transcription of four viral mRNAs. The largest mRNA (which is longer than the viral genome), is used to make the new copies of the genome and to make the capsid core protein and the viral DNA polymerase. These four viral transcripts undergo additional processing and go on to form progeny virions that are released from the cell or returned to the nucleus and recycled to produce even more copies (Bruss, 2007). The long mRNA is then transported back to the cytoplasm where the virion P protein synthesizes DNA via its reverse transcriptase activity.

-**Serotype and Genotype of HBV:** The virus has four major serotypes (adr, adw, ayr, ayw) based on antigenic epitopes presented on its envelope proteins, and its eight genotype (A-H) according to overall nucleotide sequence variation of the genome. The genotypes have a distinct geographical distribution and are used in tracing the evolution and transmission of the virus. Differences between genotypes affect the disease severity, course and likelihood of complications, and response to treatment and possibly vaccination (Kramyis et al., 2005).

Genotypes differ by at least 8% of their sequence and were first reported in 1988 when six were initially described (A – F) (Norder et al., 1994). Two further types have since been described (G and H) and most genotypes are now divided into subgenotypes with distinct properties (Kurbanov et al., 2010).

Genotype A is most commonly found in the Americans. Africa, India and Western Europe. Genotype B is most commonly found in Asia and the United States. Genotype B1 dominates in Japan, B2 in China and Vietnam while B3 confined to Indonesia. B4 is confined to Vietnam. All these strains specify the serotype aywl. B5 is most common in the philipines. Genotype C is most common in Asia and the United States. Subgenotype C1 is common in Japan, Korea and China. C2 is common in China, South-East Asia and Bangladesh and C3 in Oceania. All these strains specify the serotype adrq. C4 specifying ayw3 is found in Aborigines from Australia (Kurbanov et al., 2010). Genotype D is most commonly found in southern Europe, India and the United States and has been divided into 8 subtypes (D1-D8). In Turkey genotype D is also the most common type. A pattern of defined geographical distribution is less evident with D1-D4 where these subgenotypes are widely spread within Europe, Africa and Asia. D4 appears to be the oldest split and is still the dominating sub-genotype of D in Oceania. Type E is most commonly found in West and Southern Africa. Type F is most commonly found in Central and South America and has been divided into two subgroups (F1 and F2). Genotype G has an insertion of 36 nucleotides in the core gene and is found in France and the United States (Stuyyer et al., 2000). Type H is most commonly found in Central and South America and California in United States. Africa has five genotypes (A-E) of these the predominant genotypes are A in Kenya, B and D in Egypt, D in Tunisia, A-D in South Africa and E in Nigeria (Kurbanov et al., 2010). Genotype H is probably split off from genotype F within the New World (Arauz-Ruiz et al., 2002).

Transmission of HBV: The virus is transmitted by exposure to infectious blood or body fluids such as semen and vaginal fluids, while viral DNA has been detected in the saliva, tears and urine of chronic carriers. Perinatal infection is a major route of infection in endemic countries (Coopstead, 2010). Other risk factors include working in a healthcare setting, transfusion, dialysis, acupuncture, tattoning, extended overseas travel, and residence in an institution (Sleisenger et al., 2006). However HBV cannot be spread by holding hands, sharing eating utensils or drinking, glasses, kissing, hugging, coughing, sneezing or breast feeding. HBV can be transmitted between family members within households, possibly by contact of non-intact skin or mucous membrane with secretions containing the virus.

-**Pathogenesis:** HBV interferes primarily with the functions of the liver by replicating in the hepatocytes. The receptor is not yet known though there is evidence that the receptor in the closely related duck hepatitis B virus is carboxypeptidase D (Glebe and Urban, 2007). The virions bind to the host cell via the pre S domain of the viral surface antigen and are subsequently internalized by endocytosis. Pre- S and 1gA receptors are accused of this interaction. HBV – Pre – S – specific receptors are expressed primarily on hepatocytes, however, viral DNA and proteins have also been detected in extrahepatic sites suggesting that cellular receptors for HBV may also exist on extrahepatic cells (Fairley and Read, 2012).

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During HBV infection, the host immune response causes both hepatocellular damage and viral clearance. Although the innate immune response does not play a significant role in these processes, the adaptive immune response in particular virus-specific cytotoxic T lymphocytes (CTLs) contribute to most of the liver injury associated with HBV infection. CTLs eliminate HBV infection by killing infected cells and producing antiviral cytokines, which are then used to purge HBV from viable hepatocytes (Iannacone et al., 2007). Although liver damage is initiated and mediated by the CTLs, antigen – non specific inflammatory cells can worsen CTL – induced immunopathology and platelets activated at the site of infection may facilitate the accumulation of CTLs in the liver (Iannacone et al., 2005).

-**Epidemiology of HBV:** The primary method of transmission reflects the prevalence of chronic HBV infection in a given area. In low prevalence areas such as the continatal United States and Western Europe; injection although other factors may also be important (Redd et al., 2007). In moderate prevalence areas, which include eastern Europe, Russia and Japan, where 2-7% of the population is chronically infected, the disease is predominantly spread among children. In high prevalence areas such as China and South East Asia, transmission during childbirth is most -common, although in other areas of high endemicity such as Africa, transmission during childhood is a significant factor (Alter, 2003).

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The prevalence of chronic HBV infection in areas of high endemicity is at least 8%. As of 2010, China has 120 million infected people, followed by India and Indonesia with 40 million and 12 million respectively. And according to World Health Organization an estimated 600,000 people die every year related to the infection.

-**Acute hepatitis B virus infection:** This is associated acute viral hepatitis. This form resolves spontaneously after 4-8 weeks illness. Most patients recover without significant consequences and without recurrence. The incubation period for acute hepatitis B infection varies between 45 – 120 days with a range of 60 – 90 days (Hoofnagle and DiBisceglie, 1991). Over 90% of perinatal HBV infection are asymptomatic, while typical manifestations of acute hepatitis are noted; 5-15% of newly infected young children and 33-50% of older children, adolescents and adults (McMahon et al, 1985). The hallmark of acute viral hepatitis is the striking elevation in serum transaminases activity.

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The first serological markers to become detectable in persons with acute HBV infection are HBsAg and anti bodies to hepatitis B core antigen. Within 6-12 months post infection 1gM antibodies to HBcAg persist for life and are found in persons with chronic infection as well as those who recover from infection. The presence of anti-HBs indicates immunity to HBV infection. The icteric phase of acute viral hepatitis begins usually within 10 days of initial symptoms and jaundice becomes apparent when total bilirubin level exceeds 20 to 40mg/dl which is accompanied by hepatomegaly and splenomegaly.

II. **Chronic hepatitis B virus:** This is defined as either the presence of HBsAg in the serum for at least 6 months or the presence of HBsAg in a person who tests negative for 1gM antibodies to hepatitis B core antigen. Unlike persons who recover from acute HBV, persons

with chronic HBV infection do not develop anti-HBs, and HBsAg typically persist for decades.

There is moderate to increase inflammation histologically and high risk of progression to cirrhosis.

In the low replication phase of chronic HBV infection, there is loss of HBeAg, or a decrease or loss of the HBV DNA concentrations, and with the appearance of anti-HBe. This is termed seroconversion.

In the non replicative phase, markers of viral replication are either absent or below detection level, and the inflammation is diminished. However, if cirrhosis has already developed, it persists indefinitely (Collin et al, 2006). In cirrhosis, liver cells die and are progressively replaced with fibrotic tissue leading to nodule formation. The internal structure of the liver is deranged leading to the obstruction of blood flow and decrease in liver functions.

-**Signs and Symptoms:** Acute infection with HBV begins with general ill-health, loss of appetite, nausea, vomiting, body rashes, mild fever and dark urine, and then progreses to development of jaundice. The infection may be entirely asymptomatic and may go unrecognized (Terrault et al., 2005).

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Chronic infection with HBV may either be asymptomatic or may be associated with a chronic inflammation of the liver (chronic hepatitis), leading to cirrhosis over a period of several years. This type of infection dramatically increases the incidence of hepatocellular carcinoma. HBV has been linked to the development of membranous glomerulonephritis (MGN).

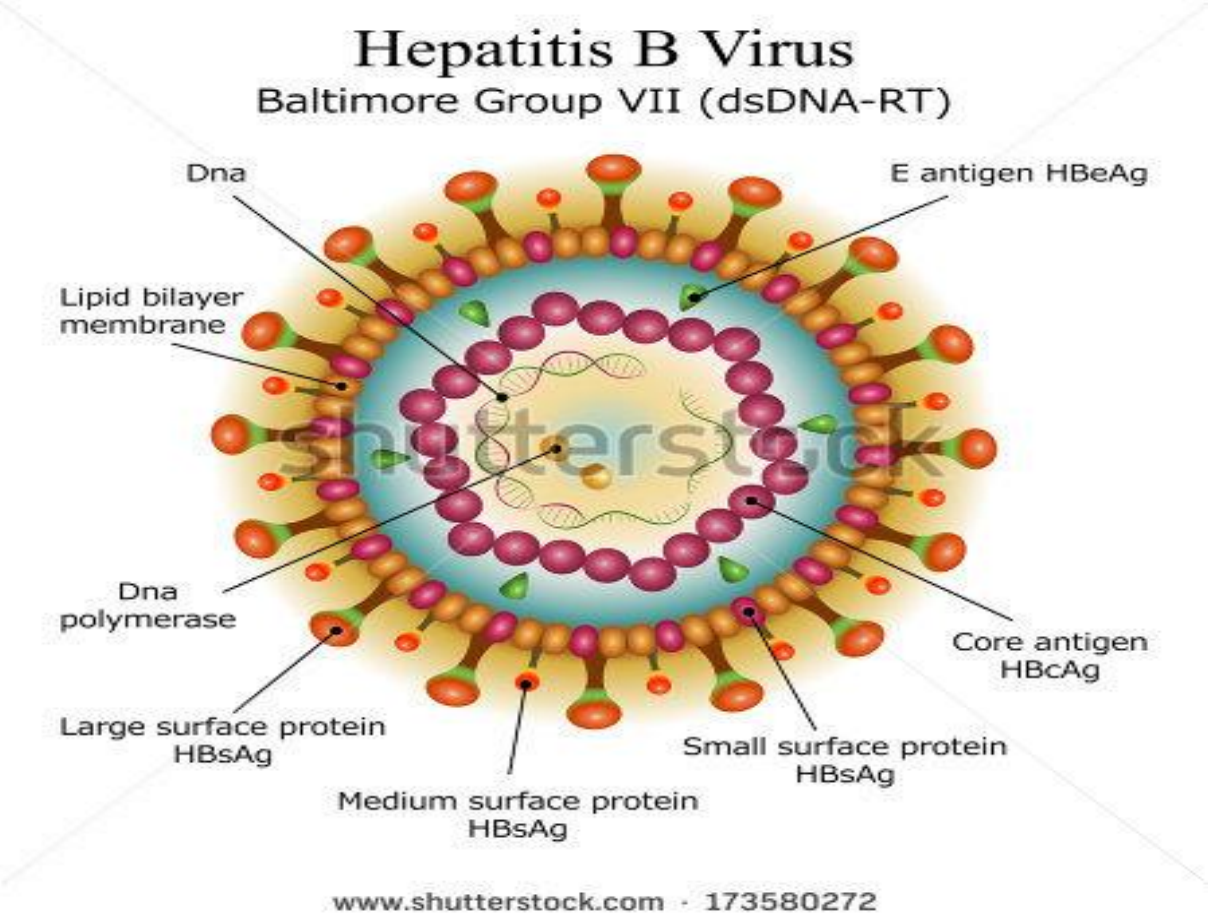

Fig 1

(Locarnini, 2004)

C. **Hepatitis C Virus (HCV):** Hepatitis C is an infectious disease affecting primarily the liver caused by the hepatitis C virus (Ryan and Ray, 2004). The infection is often asymptomatic but chronic infection can lead to scaring of the liver and ultimately to cirrhosis which is generally apparent after many years. In the face of cirrhosis it progresses to liver failure, liver cancer or life-threatening esophageal and gastric varices (Ryan and Ray, 2004).

-**History of HCV:** In the mid 1970s, Harvey J. Alter, Chief of the Infectious Disease Section in the Department of Transfusion Medicine at the National Institutes of Health, and his research team demonstrated how most post-transfusion hepatitis cases were not due to hepatitis A and B viruses. Despite this discovery, international research efforts to identify the virus, initially called non-A, non-B hepatitis (NANBH), failed for the next decade. In 1987, Michael Houghton, Qui-Lim Choo, and George Kuo at Chiron Corporation, Collaborating with Dr. D.w. Bradley at the Centre for Disease Control and prevention, used a novel molecular cloning approach to identify the unknown organism and developed a diagnostic test (Boyer, 2001). In 1988, the virus was confirmed by Alter by verifying its presence in a panel of NANBH specimens. In April 1989, the discovery of HCV was published in two articles in the journal of science. The discovery led to significant improvement in diagnosis and improved antiviral treatment (Boyer, 2001). In 2000, Drs. Alter and Houghton were honored with the Lasker Award for Clinical Medical Research.

-**Structure of HCV:** The hepatitis C virus (HCV) is a small, enveloped single – stranded positive-sense RNA virus (Rosen, 2011). It is a member of the hepacivirus genus in the family flaviviridae (Ray et al., 2009). There are seven major genotypes of HCV which are indicated numerically from one to seven (Nakano et al., 2011). In the United States, about 70% of cases are caused by genotype 1, 20% by genotype 2, and about 1% by each of the other genotypes. Genotype 1 is also the most common in South America and Europe (Nakano et al., 2011).

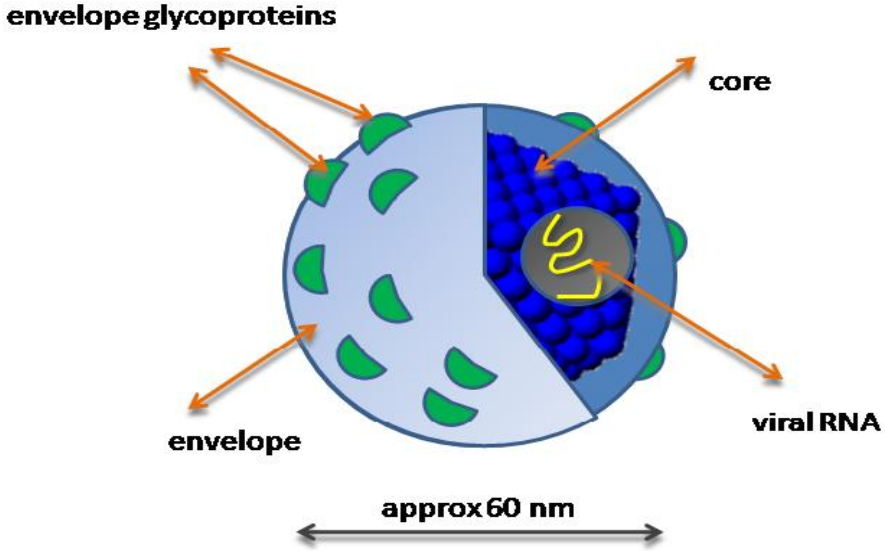

Figure 3:
(Rosen, 2011)

-**Modes of Transmission of HCV:** The primary route of transmission in the developed world is intravenous drug use (IDU), while in developing world the main routes are blood transfusion and unsafe medical procedures (Maheshwari and, Thuluvath, 2010). The cause of transmission remains unknown in 20% of cases (Ponde, 2011) however, many of these are believed to be accounted for by IDU.

A Intravenous Drug use (IDU): IDU is a major risk factor for HCV in many parts of the world (Xia *et al*., 2008). Of 77 countries reviewed, 25 (including United States) were found to have prevalence of hepatitis C in the intravenous drug user population of between 60% and 80% (Xia *et al*., 2008). Twelve (12) Countries had rates greater than 80%. It is believed that 10 million intravenous drug users are infected with HCV. China (1.6 million), United States (1-5 million), and Russia (1.3 million) have the highest absolute total (Xia *et al*., 2008). Occurrence of HCV among prison immates in the United States is 10 to 20 times that of the occurrence observed in the general population. This has been attributed to high-risk behaviour in prisons such as IDU and tattooing with non sterile equipment (Imperial, 2010).

B Healthcare Exposure: Blood transfusion or organ transplantation without HCV screening, carry significant risk of infection. Those who have experienced a needle stick injury from HCV positive patient have about 1.8% chance of subsequently contracting the disease themselves. The risk is greater if the needle in question is hollow and the puncture wound is deep (Alter, 2007). Other ways of transmission are; multiple-use of medication vials, infusion bags, and improperly sterilized surgical equipment, among others (Imperial, 2010).

C Sexual Intercourse: While there is an association between high-risk sexual activity and hepatitis C, it is not known whether transmission of the disease is due to drug use that has not been admitted to or sex as a risk factor. The majority of evidence supports there has being no risk for monogamous heterosexual couples (Tohme and Holmberg, 2010). Sexual practices that involve higher levels of trauma to the anogenital mucosa, such as anal penetrative sex, or that occur when there is a concurrent sexually transmitted infection, including HIV or genital ulceration, do present a risk (Tohme and Holmberg, 2010).

D Body Piercings: Tattooing is associated with two to threefold increased risk of hepatitis C (Jafari et al., 2010). This can be due to improperly sterilized equipment or contamination of the dyes being used. Tattoos or piercings performed either before the mid-1980's underground or nonprofessionally are of particular concern, since sterile techniques in such settings may be lacking. The risk also appears to be greater for larger tattoos (Jafari et al., 2010) as it is estimated that nearly half of prison immates share unsterilised tattooing equipment.

E Shared Personal Items: Personal care item such as razors, toothbrushes and manicuring or pedicurring equipment can be contaminated with blood. Sharing such items can potentially lead to exposure to HCV.

F Vertical Transmission: This is the mother to child transmission, which occur – in less than 10% of pregnancies (Lam et al., 2010) and there no measures that alter this risk. It is not clear when, during pregnancy transmission occurs, but it may occur both during gestation and at delivery (Ponde, 2011). A long Labour is associated with 9 greater risk of transmission (Alter, 2007). Although there is no evidence yet that breastfeeding spreads HCV but mothers are advised to avoid breastfeeding if her nipples are cracked and bleeding (Mast, 2004).

-**Epidemiology of HCV:** It is estimated that 130-170 million people, or ~ 3% of the world's population are living with chronic HCV. About 3-4 million are infected yearly and more than 350,000 people die yearly from hepatitis C-related diseases. Rates have increased substantially in 20th century due to a combination of IDU and intravenous medication or poorly sterilized

medical equipment (Ponde, 2011). Egypt has been shown to have the highest HCV prevalence globally. Among those chronically infected, the risk of cirrhosis is ~ 10% - 15% for men and ~ 1% -5% for women though the reason for this difference is not yet known. Once cirrhosis is established, the rate of developing hepatocellular carcinoma is ~ 1% - 4% per year (Yu and Chuang, 2009).

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Prevalence is higher is some countries in Africa and Asia (Holmberg et al., 2012). Countries with particularly high rates of infection include Egypt (22%), Pakistan (4.8%) and China (3.2%) (WHO, 2011). It is believed that the high prevalence in Egypt is linked to a non-discontinued mass treatment campaign for schistosomiasis using improperly sterilized glass syringes (Alter, 2007).

-**Signs and Symptoms of HCV:** Acute HCV infection are generally mild and vague in symptoms, it also causes decreased appetite, fatigue, nausea, muscle or joint pains, and weight loss and most cases of acute infection are not associated with jaundice (Nelson et al., 2011). The infection resolves spontaneously in 10-50% of cases, which occurs more frequently in individuals who are young and female (Nelson et al., 2011).

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Chronic HCV infection accounts for about 80% and most people experience minimal or no symptoms during the initial few decades of the infection although Chronic HCV can be associated with fatigue. HCV, after many years becomes the primary cause of cirrhosis and liver cancer (Rosen, 2011). About 10-30% of people develop cirrhosis over 30 years. Cirrhosis is more common in those co-infected with hepatitis B virus or HIV, alcoholics and those of male gender. Those that develop cirrhosis have a 20-folds greater risk of hepatocellular carcinoma, a rate of 1-3% per year (Rosen, 2011) and if this is complicated by excess alcohol, the risk becomes 100 fold greater (Mueller et al., 2009). Hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma worldwide (Alter, 2007).

Extrahepatic: HCV is also rarely associated with Sjogren's syndrome (an autoimmune disorder), thrombocytopaenia, lichen planus, diabetes mellitus and B – cell lymphoproliferative disorders (Zignego et al., 2007). Thrombocytopenia is estimated to occur in 0.16 to 45.4% of people with chronic hepatitis C (Louie, 2011). Hepatitis C infection is also associated with a condition called mixed cryoglobulinemia which is an inflammation of small and medium sized blood vessels caused by deposition of immune complexes involving cryoglobulines.

HAEMOSTASIS

This is a collection of complex interrelated systemic mechanisms operating to maintain balance between coagulation and anticoagulation. It is a process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system (Willian, 2003). The haemostatic mechanisms have several important functions: to maintain blood in a fluid state while it remains circulating within the vascular system, to arrest bleeding at the site of injury or blood loss by formation of a haemostatic plug, to ensure the eventual removal of the plug when healing is complete (Dacie and Lewis, 2001). There are five different components involved: blood vessels, platetets, plasma coagulation factors, their inhibitors and the fibrinolytic system.

A. MECHANISM OF COAGULATION

The central event in the coagulation pathway is the production of thrombin which acts upon fibrinogen to produce fibrin and thus the fibrin clot. This clot is further strengthened by the crosslinking action of factor XIII which itself, is activated by thrombin (Dacie and Lewis 2001).

B. ANTICLOTING MECHANISM

The tendency of blood to clot is balanced invivo by limiting reactions that tend to prevent clothing inside the blood vessels and breakdown any clots that do form. These reactions include the

interaction between the platelet-aggregating effect of thromboxane A2 and the antiaggregating effect of prostacychin, which causes clots to form at the site when blood vessel is injured but keeps the vessel lumen free of clot (Willam, 2003).

The activated partial thromboplastin time (aPTT) and the prothrombin time (PT), have been used historically to define two pathways of coagulation activation: the intrinsic and extrinsic pathways.

ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)

This is also known as the partial thromboplastin time with kaolin and the kaolin cephalin clotting time reflecting the methods used to perform the test. The test measures the clothing time of plasma after the activation of contact factors but without added tissue thromboplastin, and so indicates the overall efficiency of the intrinsic pathway.

The principle is based on the pre-incubation of the test plasma with an activator. At this phase, factor XIIa is produced which cleaves to factor XI to factor XIa but coagulation does not proceed beyond this in the absence of calcium.

After recalcification, factor XIa activates factor IX and coagulation follows. The test depends not only on the contact factors (factor XII, prekallikrein, high molecular weight kininogen) and on factors VIII and IX, but also on the reaction with factors X,V, prothrombin and fibrinogen.

However, a significant prolongation of the aPTT indicates the presence of a factor deficiency (VIII, IX, XI, XII, prekallikrein and high molecular weight kininogen), while prolongation of both the prothrombin time (PT) and aPTT suggests a deficiency of factor VII and XIII (Sahud, 2000).
The aPTT was first described in 1953 by researchers at the University of North Carolina at chapel Hill (Langdell et al., 1953).

PROTHROMBIN TIME (PT)

This provides a functional determination of the integrity of the extrinsic (tissue factor) pathway of coagulation and is sensitive to the vitamin –k dependent clotting factors (II,VII,IX and X) as well as to factors of the common pathway (fibrinogen, prothrombin, V, and X) (Jackson et al., 2003). The degree of prolongation of the clothing time correlates to the degree of deficiency or inhibition of extrinsic or common pathway clothing factors which are synthesized by the liver (Hyers et al., 2001)

HISTORY: Prothrombin Time (PT) was discovered by Dr. Armond Quick and colleagues in 1935 (Quick et al., 1935) and a second method was published by Dr. Paul Owren (Owren and Aas, 1951) also called “P and P” or prothrombin and proconvertin” method. It aided in the identification of the anticoagulants Dicumarol and Warfarin (Campbell *et al*., 1941).

THROMBIN TIME (TT)

The thrombin time measures the thrombin-induced conversion of fibrinogen to fibrin directly in patient’s plasma, bypassing all other clothing factors. A low concentration of thrombin is added directly to the citrated plasma and the time required for the formation of fibrin monomers is measured by visual, mechanical opto-electronic techniques (Jespersen and Siddmann, 1982).

The thrombin time is prolonged by thrombin inhibitors and inhibitors of fibrin formation and polymerization but not affected by problems with thrombin generation. The difference in time between the test and “normal”, indicates an abnormality in the conversion of fibrinogen to fibrin, an insoluble protein (Popovic et al., 2012)

FIBRINOGEN

Fibrinogen is a large dimericprotein, each half consisting of three polypeptides named Aα, Bß and γ held together by 12 disulphide bonds. The two monomers are joined together by a further

three disulphide bonds. Fibrinogen has a molecular weight of 340k Da (Dacie and Lewis, 2001). The N-terminal sections of these three chains contain the cysteines that participate in the cross-linking of the chains. The C-terminal parts of theα, ß and γ chains contain a domain of about 225 amino acid residues, which can function as a molecular recognition unit (Muszbek et al., 2008). In fibrinogen as well as in angiopotin, this domain is implicated in protein-protein interactions. In lectins, such as mammalian ficolins and invertebrate tachylectin SA, the fibrinogen C-terminal domain binds carbohydrates. On the fibrinogen α and ß chains, there is a small peptide sequence (called a fibrinopeptide). These small peptides are what prevents fibrinogen from spontanrusly forming polymers with itself (Acharya and Dimichele, 2008).

Fibrin is formed from fibrinogen by thrombin cleavage of the A and B peptides from fibrinogen. This results in fibrin monomers that associate to form a polymer. That is the visible clot. The central E domain exposed by thrombin cleavage binds with a complementary region on the outer or D domain of another monomer. The monomers then, assemble into a staggered overlapping two-stranded fibril (Dacie and Lewis, 2001).

The quantitative determination of plasma fibrinogen is essential in the diagnosis and management of many coagulopathies. In addition, since plasma fibrinogen levels are increased in some patients who develop myocardial infarction and stroke, there is an interest in the measurement of fibrinogen for thrombotic risk assessment (Lowe et al., 2004)

PLATELET

Platelets or thrombbocytes are small fragments of cytoplasm with diameter of 203 nm which are derived from fragmentation of precursor megarkaryocyte (Campbell, 2008). The average life span of platelets is normally just 5 to 9days. They are a natural source of growth factors and are involved in hemostasis, leading to the formation of blood clot as they circulate in the blood of mammals.

If the number of platelets is too low, excessive bleeding can occur. However if the number is too high, blood clots can form (thrombosis), which may obstruct blood vessels and result in stroke, myocardial infarction, pulmonary embolism etc. An abnormality or disease of the platelets is called thrombocytopathy which could be either a low number or platelet (thrombocytopaenia), a decrease function of platelet (thrombasthaenia) or an increase in the number of platelets (thrombocytosis) (Maton et al., 1993).

Discovery: Although red blood cells had been known since Van leeunhock (1632-1723), the German anatomist Max Schultze (1825-1874) was the first to describe platelets (Brewer, 2006). He described “spherules” that were much smaller than red blood cells and that occasionally clumped and were found in collections of fibrous materials.

GiulioBizzozero (1846-1901), building on Schultze’s findings. used “ living Circulation” to study blood cells of amphibians microscopically invivo. He is especially noted for discovering that platelets clump at the site of blood vessel injury, a process that precedes the formation of a blood clot. This observation confirmed the role of platelets in coagulation.

Activation of platelets: The inner surface of the blood vessels is lined with a thin layer of endothelial cells that, in normal hemostasis, act to inhibit platelet activation by producing nitric oxide, endothelial-ADPase, and PGI2. Endothelial-ADPase clears away the platelet activator. ADP Endothelial cells produce a protein called van Willebrand factor (VWF), a cell adhesion ligand, which helps endothelial cells adhere to collagen in the basement membrane. VWF is secreted constitutively into the plasma by the endothelial cell and is stored in granules within the endothelial cells and in platelets (Brewer, 2006).

When the endothelial layer is injured, collagen, VWF and tissue factor from the subendothelium are exposed to the bloodstream. When the platelet contact collagen or VWF, they are activated, hence clump together. (Kroll and Hellum, 1996).

Adhesion and Aggregation of Platelets: Platelets aggregate or clump together, using fibrinogen and von Willebrand factor (VWF) as a connecting agent. The most abundant platelet aggregation receptor is glycoprotein IIb/IIIa (calcium-dependent receptor of fibrinogen), fibronectin, vitrorectin, thrombospontin and VWF. Others include GPIb-V-IX complex.

Activated platelets will adhere via glycoprotein (GP) 1a to the collagen that is exposed by endothelial damage. Aggregation and adhesion act together to form the platelet plug. Myosin and actin filaments in platelets are stimulated to contract during aggregation, further reinforcing the plug. Platelet aggregation is stimulated by ADP, thromboxane, and $\alpha 2$ receptor-activation, but inhibited by other inflammatory products, like PGI2 and PGD2. Platelet aggregation is enhanced by exogenous administration of anabolic steroids (kroll and Hellum, 1996).

FATE OF COAGULATION IN LIVER DISEASES

The liver plays a major role in haemostasis as most of the coagulantion factors , anticoagulant proteins and components of the fibrinolytic system are synthetised by the hepatic parenchymal cells. But when the liver is diseased, these functions are impaired.

The actiology of impaired haemostasis resulting from abnormal liver function is often multifactorial and may include impaired coagulation factors synthesis, consumption of coagulation factors, altered clearance of activated coagulation factors and quantitative and qualitative platelet disorders (Pereira et al., 1996).

A. coagulation defects in acute liver diseases: In acute liver disease, Commonly, the vitamin k - dependent factors decrease first. Staring with factor VII and protein c owing to their short half-life (6hrs), followed by reductions factors II and X levels. Factor V levels are decreased in both acute and chronic liver diseases (Mammen, 1994). Factor IX levels are usually only modestly reduced until advanced stages of liver disease. In contrast, VWF and factor VII levels may be normal even in the presence of advanced liver disease because there is an increased production of factor VIII by Sinusoidal endothelial cells when the liver is damaged; combined with decreased clearance of the VWF/ factor VIII complex (Mammen, 1994)

Fibrinogen levels are rarely decreased and may even be elevated because of abnormal non-functional fibrinogen related to defective polymerization. A. decrease in fibrinogen levels may indicate the presence of disseminated intravascular coagulation (DIC) or progression to fulmmaint hepatitis with hepatic failure (Kerr, 2003). There are gross abnormalities of the fibrinolytic system in fulmmant liver failure but because inhibitory activity appears to be present in adequate quantities, this limits the incidence of bleeding due to fibrinolysis (Pernambuco et al; 1993).

B: COAGULATION DEFECTS IN CHRONIC LIVER DISEASES:

Most coagulation factors and inhibitors of the coagulation and fibrinolytic system are markedly reduced in liver cirrhosis because of impaired protein synthesis, except for factor VIII and fibrinogen levels, which may be normal or increased. Possible explanations for the increased factor VIII levels are the increased hepatic biosynthesis of vWF and decreased expression of low-density lipoprotein receptor –related protein, both of which modulate the levels of factor VIII in plasma, rather than increased factor VIII synthesis (Hollestelle et al, 2004). Because fibrinogen is an acute- phase reactant, its synthesis tends to be preserved in patients with stable cirrhosis.

The deficiency of vitamin K-dependent factors in cirrhosis may occur by several mechanisms, including reduced hepatic synthesis and reduced absorption of Bile salts required for absorption of vitamin K-dependent factors, which may occur in setting of cholestatic liver diseases. Other contributing factors include poor oral intake and treatment with antibiotics that destroy the intestinal bacterial that synthesis vitamin K. As with acute liver diseases, the reduction in coagulation factors parallel the degree of progression of liver diseases (Kujovich, 2005). In addition to the reduced hepatic synthesis of clotting factors, cirrhotic patients also have a significant deficit of natural anticoagulants, particularly proteins and antithrombin (Castelino and Salen, 1997).

C.PLATELET FUNCTION ABNORMALITIES:

In the face of chronic liver diseases, there is impaired platelet aggregation with different agonists including adenosine diphosphate (ADP), thrombin, epinephrine and ristocetin (Ogasawara et al., 2005). The abnormal platelet aggregation is thought to be caused by circulating platelet inhibitors(fibrin degradation products and D-dimers), plasmin degradation of platelet receptors, dysfribrinogenenemia and excess nitric oxide synthesis (Kujovich, 2005). Conversely, hyper-responsiveness rather than a defective platelet/vwF interaction is observed in cirrhosis, which may compensate for other haemostatic problems; this appears to be mediated primarily by increased vwF levels (Beer et al., 1995). The platelet function defect may account for the prolongation of the bleeding time in 40% of patients with cirrhosis and correlates with diseases severity (Homoncik et al., 2004).

FREE RADICALS AND LIVER DISEASES

Reactive oxygen and nitrogen species (ROS and RNS) are produced by metabolism of normal cells. However, in liver diseases, redox is increased thereby damaging the hepatic tissue; the capability of ethanol to increase both ROS/RNS and peroxidation of lipids, DNA, and proteins was demonstrated in a variety of systems, cells, and species, including humans. ROS/RNS can activate hepatic stellate cells, which are characterized by the enhanced production of extracellular matrix and accelerated proliferation. Cross-talk between parenchymal and nonparenchymal cells is one of the most important events in liver injury and fibrogenesis; ROS play an important role in fibrogenesis throughout increasing platelet-derived growth factor. Most hepatocellular carcinomas occur in cirrhotic livers, and the common mechanism for hepatocarcinogenesis is chronic inflammation associated with severe oxidative stress; other risk factors are dietary aflatoxin B_1 consumption, cigarette smoking, and heavy drinking. Ischemia–reperfusion injury affects directly on hepatocyte viability, particularly during transplantation and hepatic surgery; ischemia activates Kupffer cells which are the main source of ROS during the reperfusion period. The toxic action mechanism of paracetamol is focused on metabolic activation of the drug, depletion of glutathione, and covalent binding of the reactive metabolite *N*-acetyl-*p*-benzoquinone imine to cellular proteins as the main cause of hepatic cell death; intracellular steps critical for cell death include mitochondrial dysfunction and, importantly, the formation of ROS and peroxynitrite. Infection with hepatitis C is associated with increased levels of ROS/RNS and decreased antioxidant levels. As a consequence, antioxidants have been proposed as an adjunct therapy for various liver diseases (Pablo, 2009).

CIRRHOSIS AND FREE RADICALS

Liver fibrosis is the result of an exacerbated wound-healing process after chronic hepatic damage and is characterized by the activation of hepatic stellate cells (HSC) and excess production of extracellular matrix (ECM) components by these cells. The activation of HSC involves the transdifferentiation from a quiescent state into myofibroblast-like cells. The activated HSC are characterized by the enhanced production of ECM and accelerated proliferation.

The embryologic origin of stellate cells has been elusive. Currently, the bulk of evidence supports their origin from either the endoderm or the septum transversum, as it forms from cardiac mesenchyme during invagination of the hepatic bud (Friedman, 2008).

VIRAL HEPATITIS AND FREE RADICALS

Infection with HCV is associated with increased levels of ROS/RNS and decreased antioxidant levels in patients. Patients infected with HCV show increases in lipid peroxidation levels in liver samples, serum, and peripheral blood mononuclear cells. In addition, other indicators of oxidative stress such as 4-hydroxynonenal and 8-hydroxydeoxyguanosine were found to be increased in HCV. The content of GSH decreased in the blood, liver, and lymphatic system, whereas that of GSSG increased, indicating a high glutathione turnover (Choi et al, 2006).

The presence of ROS and RNS is, interestingly, more pronounced with HCV than with HBV. The mechanisms for more severe increases of oxidative and nitrosative stresses during HCV disease may include chronic inflammation (i.e., phagocytic NAD(P)H oxidase activation) and overload of iron, which is more specific to HCV. Furthermore, the production of ROS in the hepatocytes may lead to the activation of KC. These cells, when activated, produce and secrete cytokines; cytokines may be proinflammatory, such as TNF-α and IL-1, or profibrotic, such as TGF-β. These proteins can further increase ROS and play important roles in the mediation of hepatic injury, such as fatty liver, by inhibiting lipase of lipoprotein and adiponectin and fibrosis as a result of HSC activation (Poli, 2000).

In addition, proteins of HCV can increase ROS and RNS in the infected cells; proteins of the HCV core have been shown to augment the oxidative and nitrosative stress, lipid peroxidation, oxidized thioredoxin, and antioxidant gene expression such as that of metallothionein family proteins and manganese superoxide dismutase (MnSOD) as well as to enhance sensitivity to toxins such as ethanol and CCl_4 (Abdalla et al, 2005). HCV core gene expression diminishes the intracellular GSH levels and the mitochondrial NADPH content that are associated with increased uptake of calcium and oxidative stress generation at complex I in mitochondria, providing an action mechanism for HCV-induced ROS production (Moriah et al., 2001).

Nonstructural proteins may also modulate the host redox status by HCV. Host antioxidant defenses, such as GSH, catalase, MnSOD, and heme oxygenase-1, are augmented, suggesting adaptation to ROS/RNS stress (Gong et al., 2001). Stress produced by ROS/RNS has been implicated in HCV-induced hepatic cancer. HCV core-induced iNOS generates RNS, which may cause damage to the DNA, and augments mutations within the immunoglobulin and tumor suppressor genes. The genotoxic effects of ROS/RNS may contribute to the development of B-cell lymphoma or HCC during HCV infection. In fact, this association was documented in vivo in HCV core-transgenic mice. Other mechanisms by which core protein increases HCC include the modulation of tumor suppressor genes and proto-oncogenes as well as the inhibition of apoptosis. In this regard, it should be noted that oxidative and nitrosative stress may possess diverse effects on cell growth and apoptosis. As a consequence, antioxidants have been proposed as an adjunct therapy for chronic hepatitis C (Melhem et al, 2005).

Conclusion

Hepatitis is a medical condition which is defined by the inflammation of the liver and characterized by the presence of inflammatory cells in the tissue of the organ which can be self-limiting or progress to fibrosis and cirrhosis. Inflammation of the liver can be viral or non-viral. It is called viral when viruses are associated with the inflammation e.g. Hepatitis A virus, Hepatitis B virus and Hepatitis C virus. It is called non Viral when other factors are involved via; alcohol, organic solvents, infections, autoimmune

diseases, drugs toxins etc. This is a collection of complex interrelated systemic mechanisms operating to maintain balance between coagulation and anticoagulation. It is a process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system. Most coagulation factors and inhibitors of the coagulation and fibrinolytic system are markedly reduced in liver cirrhosis because of impaired protein synthesis, except for factor VIII and fibrinogen levels, which may be normal or increased. The deficiency of vitamin K-dependent factors in cirrhosis may occur by several mechanisms, including reduced hepatic synthesis and reduced absorption of Bile salts required for absorption of vitamin K-dependent factors, which may occur in setting of cholestatic liver diseases. As with acute liver diseases, the reduction in coagulation factors parallel the degree of progression of liver diseases

References

Abdalla MY, Ahmad IM, Spitz DR, Schmidt WN, Britigan BE. Hepatitis C virus-core and non structural proteins lead to different effects on cellular antioxidant defenses. *J Med Virol. 2005;* **76**:489–497.

Acharya, S.S., and Dimichele ,D.M. (November, 2008), "Rare Inherited DisordersofFibrinogen." *Haemophilia*: The Official Journal of the World Federation of Hemophilia **14** (6): 1151 – 8.

Alter, H.J., and Blumberg, B.S., (March 1966). "Further studies on a "new" human isoprecipitin system (Australia antigen)".*Blood* **27** (3): 297-309.

Alter, M.J., (2003) "Epidemiology and the Prevention of Hepatitis B: *Seminars in Liver Disease."* **23 (**1): 39 – 46.

Alter, M.J., (2007) "Epidemiology of hepatitis C virus infection" *World journal of gastroenterology:* **13** (17): 2436-41

Aragones, L., Bosch, A., and Pinto, R.M., (February 2008). "Hepatitis A Virus Mutant Spectra under the Selective Pressure of Monoclonal Antibodies: Codon Usage Constaints Limit Capsid Variability." *J Virol **82(**4**):**1688-700.

Aragones, L., Guix, S., Ribes, E., Bosch, A., and Pinto, R.M., (March 2010). "Fine-Tuning Translation Kinetics Selection as the Driving Force of Codon Usage Bias in the Hepatitis A Virus Capsid*." Plops Pathog.* **6** (3):.

Arauz-Ruiz, P., Norder, H., Robertson, B.H., and Magnius, L.O., (August 2002). "Genotype H: A New American genotype of hepatitis B virus revealed in Central America". *J. Gen. Virol.* **83** (Pt 8): 2059-73.

Beer, J.H., Cierici, K., and Baillod, P., (1995). Quantitative and qualitative analysis of platelet GPIb and von Willebrand factor in liver cirrhosis. *Thromb Haemost* **73**(4),601-609.

Boyer, J. L., (2001). Liver Cirrhosis and its Development: Proceedings of the Falk Symposium 115. *Springer*. Pp.344.

Brewer, D.B., (2006) "Max Schultze (1865), G. Bizzozero (1882) and the Discovery of platelets".*British Journal Heamatology **133(**3**):** 251-258.*

Brundage, S.C., and Fitzpatrick, A.N., (2006). "Hepatitis A." *Am Fam Physician* **73** (12): 2162 – 8.

Bruss, V., (January 2007). "Hepatitis B virus morphogenesis". *World .J. Gastroenterol* **13**(1); 65-73.

Campbell, H.A., Smith, W.K., Roberts, W.L., and Link, K.P., (1941). Studies on the hemorrhagic sweet clover disease. *Journal of Biology and Chemistry***138**:1-20.

Campbell, N.A., (2008). "Biology" 8th edition Pearson Education Publishes London p. 912.

Castelino, D.J., and Salem, H.H., (1997). Natural Anticoagulants and the Liver. *J Gastroenterol Hepatol* **12** (1): 77 – 83.

Centers for Disease Control and Prevention (CDC). Retrieved **2011**-11-29.

Ching, K.Z., Nakano, T., Chapman, L.E., Demby, A., and Robertson, B.H., (2002)."Characterization of Wild-type Genotype V11 Hepatitis A Virus." *J Gen Virol* **83** (1):53 – 60.

Choi J, Ou JH. Mechanism of liver injury: III. Oxidative stress in the pathogenesis of hepatitis C virus. *Am J Physiol Gastrointest Liver Physiol. 2006*; **290**: G847–G851.

Connor, B.A., (2005). "Hepatitis A Vaccine in the Last-minute Traveller." *Am J med*. **118** (Suppl 10 A): 58S – 62S.

Coopstead, and Lee-Ellen, C., (2010). Pathophysiology. Missouri: Saunders, p.p., 886-887.

Cristina, J., and Costa – Mattioli, M., (August 2007), "Genetic Variability and Molecular Evolution of Hepatitis A Virus." *Virus Res*. **127** (2): 151 – 7.

Dacie and Lewis (2001)"Haemostasis" In test book of practical Haemetology. 9th Edition. Ed: Lewis, S.M., Bain, B.J., and Bates, I.) Churchill Livingstone London **pp** 339-342.

Dane, D.S., Cameron, C.H., and Briggs, M., (April 1970). "Virus-like particles in serum of patients with Australia-antigen-associated hepatitis". *Lancet **1***(7649): 695-8.

De Paula, V.S., Baptista, M.L., Lampe, E., Niel, C., and Gasper, A.M., (2002). "Characterization of Hepatitis A Virus Isolates from Sub genotypes 1A and 1B in Rio de Janeiro, Brazil." *J. med. Virol* **66** (1): 22 - 27.

Fairley, C.K., and Read, T.R., (February 2012). "Vaccination against sexually transmitted infections". *Current Opinion in Infectious Diseases* **25**(1): 66-72.

Friedman SL. Hepatic stellate cells: protean multifunctional, and enigmatic cells of the liver. Physiol Rev. 2008;**88**:125–172.

Galibert, F., Mandart, E., Fitoussi, F., Tiollais, P., and Charnay, P., (October 1979). "Nucleotide sequence of the hepatitis B virus genome (subtype ay w) cloned in E. coli". *Nature* **281** (5733): 646-50.

Gimson, A. E., (July 1996). "Fulminant and Late Onset Hepatic Failure." *Br J. Anaesth* **77** (1): 90 – 8.

Glebe, D., and Urban, S., (January 2007). "Viral and cellular determinants involved in hepadnaviral entry". *World J, Gastroenterol.* **13** (1): 22-38.

Gong G, Waris G, Tanveer R, Siddiqui A. Human hepatitis C virus NS5A protein alters intracellular calcium levels, induces oxidative stress, and activates STAT-3 and NF-kappa B. *Proc*

Natl Acad Sci USA. 2001;**98**:9599–9604.

Harrison, T., (2009). Desk Encyclopedia of General Virology. Boston: Academic Press, p. 455.

Hayashi, H., Narita, R., Hiura, M., *et al*. (2011). "A case Study of Adult Autoimmune hepatitis with histological features of giant cell hepatitis." *Intern Med*. **50** (4): 315 – 9.

Hollestelle, M.J., Geertzen, H.G., and Straatzburg, I.H., (2004). Factor V111 Expression in Liver Disease. *Thromb Hacmost* **91** (2): 267 – 275.

Holmberg, Scott, Brunette, Gary, W., Kozarsky, Phyllis, E., Magill Alan, J., et al. eds, CDC Health Information for International Travel 2012. New York: Oxford University Press. p 231.

Homoncik, M., Hlma-Storilawetz, P., and Schmid, M., (2004). Erythropoietin increases platelet reactivity and platelet counts in patients with alcoliolic Liver cirrhosis: *a* randomised, double-blind, placebo-controlled study. *Ahment Pharmocot Ther* **20**(4), 437-413.

Howard, C. R., (1986). "The Biology of Hepadnaviruses". *Journal of General Virology* **67** (7): 1215-1235.

Houghton, M., (November 2009). "The long and winding road leading to the identification of the hepatitis C virus". *Journal of Hepatology* **51**(5): 939-48.

Hyers, T.M., Agneli, G., and Hill, R.D., (2001). Antithrombotic theraphy for venous thromboembolic disease. *Chest:* **119:** 176-193.

Imperial, J.C., (2010). "Chronic hepatitis C in the state system; insight into the problems and possible solution". *Expert review of gastroterology & hematology* **4**(3):355-364.

Jackson, C.M., Esnouf, M.P., and LindahI, T.L., (2003). A critical evaluation of the prothrombin time for monitoring oral anticoagulant therepy. *Pathphysiol Heamost Thromb* **33**(1):43-51.

Jacobson and Wiersma S., (2010). "Hepatitis A Virus Seroprevalence by Age and World Region. 1990 and 2005. " *Vaccine* **28** (41): 6653 – 7.

Jacobson, K.H., and Koopman, J.S., (2005). The Effects of Socio-economic Development on worldwide Hepatitis A Virus Seroprevalence Patterns ." *Int J Epidemiol* **34** (3): 600 – 9.

Jafari, S., Copes, R., Baharlou, S., Etminan, M., and Buxton, J., (2010). "*Tattooing and the risk of transmission of* hepatitis C a systematic review and meta-analysis". "International journal of infectious disease: *IJID:* official publication of the International Society for infection Diseases **14**(11):928-40.

Jespersen, J., and Sidelmann, J., and (1982). A study of the condiditons and accuracy of the thrombin time assay of plasma fibrinogen. *Acta Heamatol* **67**(1):2-7**.**

Kay, A., Zoutim, F., (2007). "Hepatitis B virus genetic variability and evolution". *Virus Research* **127** (2): l'64-l 76.

Kerr, R., (2003). New Insights into Haemostasis in Liver Failure. Blood . Coagul Fibrinolysis **14** (Suppl 1), S43 – 45.

Kirsch, R., Yap, J., Roberts, E.A., and Cutz, E., (April 2009). "Clinicopathologic Spectrum of Massive and Submassive Hepatic Necrosis in Infants and Children." *Hum Pathol*. **40** (4): 516 – 26.

Kramvis, A., Kew, M., and Francois, G., (March 2005). "Hepatitis B virus genotypes". V*accine* **23** (19): 2409-23,

Kroll, M., and Hellum, J., (1996) "Platetes and shear stress *Blood* 88 **(5)** 1525-1541.

Kubanov, F., Tanaka, Y., and Mizokami, M., (January 2010). "Geographical and Genetic Diversity of the Human Hepatitis B Virus" *Hepatology Research: the Official Journal of the Japan Society of Hepatology **40** (1): 14 – 30.*

Kujowich, J.I., (2005). Hemostatic Defects in End Stage Liver Disease. *Crit Care Clin* **21** (3): 563 – 587.

Lam, N.C., Gotsch, P.B., and Langan, R.C., (2010). " Caring for pregnant women and newborns with HepatitisB or C" American Family Physician **82**(10):1225-9.

Lannacone, M., Sitia, G., Ruggeri, Z.M., and Guidotti, L.G., (April 2007). "HBV Pathogenesis in Animal Models: Recent Advances on the Role of Platelets". *J. Hepatol.* **46** (4): 719-26.

Lannacone, M., Sitia, G., Isogawa, M., Marchese, P., Castro, M.G., Lowenstein, P.R.,Chisari, F.V., Ruggeri, Z.M., and Guidotti, L.G., (November 2005). "Platelets mediate cytotoxic T Lymphocyte-Induced Liver Damage." *Nat. Med.* **11** (11); 1167-9.

Lees, D., (2000). "Viruses and Bivalve Shellfish." *Int. J. Food Microbiol*. **59** (1-2): 81 – 116.

Li, W., Miao, X., Qi, Z., Zeng, W., Liang, J., and Liang, Z., (2010). "Hepatitis B virus X protein upregulates HSP90alpha expression via activation of c-Myc in human.hepatocarcinoma Cell line. Hep G2". *Virol. J.* **7**.

Lim, J.R., Faught, P.R., Chalasani, N.P., and Molleston, J.P., (2006). Severe Liver Injury After Initiating Therapy with Atomoxetin in Two Children." *J Pediatr.* **148** (6): 831 – 4.

Locarnini, S., (2004). "Molecular virology of hepatitis B virus". *Semin. Liver Dis.* **24** Suppl 1: 3 – 10

Longdell, R.D., Wagner, R., and Brinkhous, K.M., (1953). Effect of antihemophilic factors on one-stage clotting tests, a presumptive test for hemophilia and a simple one-stage antihemoplilic factor assay procedure. *Journal of Laboratory and Clinical medical 41 **(4)** 637-647.*

Louie, K.S., Micallef, J.M., Pimenta, J.M., and Forssen, U.M., (2011). "Prevalence of thrombocytopenia among patience with chronic hepatitis C: a systematic review". *Journal of viral hepatitis* **18** (1):1-7

Lv, Y.F., (2006). The Coagulation Disorder of Liver Disease. *Journal of Coagulation*. **5**: 47 – 50

Lowe, G.D., Rumley, A., and Mackie, I.J., (2004) Plasma fibrinogen. *Ann Clin Biochem* **41**(pt 6):430-440.

MacCallum, F.O., (1947). "Homologous serum hepatitis". *Lancet* **2**.

Machida K, Cheng KT, Sung VM, Lee KJ, Levine AM, and Lai MM. hepatitis C virus infection activates the immunologic (type II) isoform of nitric oxide synthase and thereby enhances DNA damage and mutations of cellular genes. *J Viro* **l 78**:8835-8843, 2004.

Mahaeshwari, A., and Thuluvath, P.J., (2010). "Management of acute hepatitis C" Clines in liver disease ***14*** *(1):169-76.*

Mammen, E.F., (1994). Congulation Defects in Liver Disease. *Med Clin North Am* **78** (3), 545 – 554.

Mast, E.E., (2004). "Mother-to-infant Hepatitis C virus transmission and breastfeeding" *Advances in Experimental medicine and biology* **554:*211-6***

Maton, A., Jean, H., Charles, W.M., Susan, J., Maryanna, Q. W., David, L.H., and Jill, D.W., (1993). Human Biology and Health. 1st Edition. Englewood CliffNew Jersey: Prentice Hall p. 116-120.

Melhem A, Stern M, Shibolet O, Israeli E, Ackerman Z, Pappo O, et al. Treatment of chronic hepatitis C virus infection via antioxidants: results of a phase I clinical trial. *J Clin Gastroenterol*. 2005; **39**: 737–742.

Moreno, A., Perez-Elias, M.J., Quereda, C., Fernandez-Munoz, R., ,Antela, A., Moreno, L., Barcena, R., Lopez- san Roman, A., Celma, M.L., Gracia-Martos, M., and Moreno, S., (2006). "Syncytial giant cell hepatitis in human immunodeficiency virus-infected patients with chronic hepatitis C: 2 cases and review of the literature"Human Pathology **37**(10): 1344-9.

Moriya K, Nakagawa K, Santa T, Shintani Y, Fujie H, Miyoshi H, et al.Oxidative stress in the absence of inflammation in a mouse model for hepatitis C virus-associated hepatocarcinogenesis. Cancer Res. 2001**; 61**: 4365–4370.

Mueller, S., Milloing, G., and Seitz, H.K., (2009). Alcoholic liver disease and hepatitis and C a frequency underestimated combination (PDP) I *World journal of gastroenterology WJG* **15** (25): 3462-71

Muszbek L, Bagoly Z, Kotona E (Year 2008), "The involvement of blood coagulation factor XIII in fibrinolysis and thrombosis." Cardiovascular & Hematological Agents in Medicinal Chemistry
6 (3): 190-205.

Murray. P. R., Rosenthal. K.S. & Pfaller, M. A. (2005) Medical Microbiology 5th Ed. Elsevier Mosby.

Nadir, A., Reddy, D., Van Thiel, D.H., (2000). "Cascara Sagrada-Induced Intrahepatic Cholestasis causing portal hypertension: case report and review of herbal hepatotoxicity." *Am J. Gastroenterol* **95** (12): 3634 – 7.

Nakanuma, Y., Sasaki, M., Terada, T. and Harada, K., (1994). Intrahepatic Peribiliary Glands in Humans. 11. Pathological Spectrum." *J Gastroenterol Hepatol***. 9** (1): 80 – 6.

Nakano, T., and Lau, G.M., (2011). "An updated analysis of hepatitis C virus genotypes and subtypes based on the complete coding region". *Liver Int*. **32** (2): 339-45

Nakano, T; Lau, GM; Lau, GM et al. (December 2011). "An updated analysis of hepatitis C virus genotypes and subtypes based on the complete coding region". *Liver Int*.**32** (2): 339–45.

Nelson, PK; Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, Degenhardt L (2011-08-13).

Norder, H., Courouce, A.M., and Magnius, L.O., (1994). "Complete genomes, phylogenic relatedness and structural proteins of six strains of the hepatitis B virus, four of which represent two new genotypes". *Virology* **198** (2): 489-503.

Ogasawara, F., Fusegawa, H., and Haruki, Y., (2005). Platelet Activation in Patients with Alcoholic Liver Disease. *Tokai j. Exp Clin Med*. **30**(1): 41 – 48.

Owren, P.A., and Aas, K., (1951). The Control of dicumarol therapy and the quantitative determination of prothrombin and proconvertin.*Scandalivan journal of clinical Laboratory and investigations 3**(3):** 201 – 208.*

Pereira, S.P., Langley, P.G., and Williams., R., (1996). The Management of Abnormalities of Hemostasis in Acute Liver Failure.*Semin Liver Dis* **16** (4), 403 – 414.

Pablo, M.,(2009) the role of free radicals in liver diseases.*Hepatol int. **3**(4):526-536.*

Pernambuco, I.R., Langley, P.G., and Hughes, R.D., (1993). Activation of the Fibrinolytic System in Patients with Fulminant Liver Failure. *Hepatology* **18** (6) 1350 -1356.

Poli, G., (2000). Pathogenesis of liver fibrosis: role qxidation stress *molecular Aspect of medicine* **21** : 49-98.

Ponde, R.A., (2011). "Hidden hazard of HCV transmission". *Medical microbiology and immunology* **200**(1):7-11.

Popovic, M., Smiljanic, K., Dobutovic, B., Syrovets, T., Simmet, T., and Isenovic, E.R(2012). "Thrombin and vascular inflammation". *Molecular and Cellular* Biochemistry **359** (1-2): 301-13.

Roche B, and Samuel D. (January 2011). "The difficulties of managing severe hepatitis B virus reactivation". *Liver International: Official Journal of the International Association for the Study of the Liver* **31** Suppl 1: 104-10.

Quick, A., J., Stanley-Brown, M., and Bancroft, F.W., (1935). A study of the coagulation defect in hemophilis and in Jaundice. *America Journal of medical science **190**:50*1.

Ray, Stuart C.; Thomas, David L. (2009). "Chapter 154: Hepatitis C". In Mandell, Gerald L.; Bennett, John E.; Dolin, Raphael. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* (7th ed.). Philadelphia, PA: Churchill Livingstone.

Redd, J.T., Baumbach, J., Kohn. W., Nainan, O., Khristova, M., and Williams, I., (May 2007). "Patient-to-patient transmission of hepatitis B virus associated with oral surgery",J *Infect. Dis*. **195**(9): 1311 – 4

Rosen, H.R., (2011). Clinical practice. Chronic hepatitis C infection." *The New England journal of medicine* **364**(25): 2429-38.

Ryan, K.J., and Ray, C.G., (2004). Sherris Medical Microbiology(4th ed.). McGraw Hill. Pp. 551-2.

Ryder, S., and Beckingham, I., (2001). "Acute Hepatitis. *BMJ **332*** (7279): 151 – 153.

Sahud, M.A., (2000). Factor VIII inhihibitors. Laboratory diagnosis of inhibitors. *Semin Thromb Hemost* **26**(2):195-203.

Selves ,J., Kamar, N., Mansuy, J.M., and Peron, J.M., (December, 2010). ["Hepatitis E. Virus: A New Entity"] (In French) *Ann Pathol* **30** (6): 432 – 8.

Sleisenger, MH; Feldman M, Firedman LS (2006). Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management (8th ed.). Philadelphia: Saunders.

Steffen, R., (October, 2005). "Changing Travel-related Global Epidemiology of Hepatitis A." *Am J. med*. **118** (Suppl 10A): 46S – 49S.

Stuyver, L., De Gendt, S., and Van Geyt, C., (January 2000). "A New Genotype of Hepatitis B Virus: Complete Genome and Phylogenetic Relatedness." *J Gen Virol* **81** (Pt 1): 67 - -74.

Terrault, N., Roche, B., Samuel, D. (July 2005). "Management of the hepatitis B virus in the liver transplantation setting: a European and an American perspective". *LiverTranspl.***11** (7): 716–32.

Tohme, R.A., and Holmberg, S.D., (2010). "Is sexual contact a major mode of hepatitis C virus transmission". *Hepatology* **52**(4):1497-505.

Vine, AK.Recent advances in haemostasis and thrombosis. Retina. 2009;**29**(1):1-7(8)

Wanless, I.R., (September, 1995). "Terminology of Nodular Hepatocellular Lesions." *Hepatology* **22** (3): 983 – 993.

Whetter, L.E., Day. S.P., Elroy – Stein, O., Brown, E.A., and Lemon, S.M., (August 1994). "Low Efficiency of the 5 nontranslated Region of Hepatitis A Virus RNA in directing cap – independent translation in permissive monkey kidney cells." *J Virol*. **68** (8): 5253 – 63.

William, F.G., (2003). Haemostais" In textbook of review of Medical Physiology.21st Edition.McGrawhill. p. 543-546.

Williams, R., (2006). "Global Challenges in Liver Disease." Hepatology (*Baltimore, md*) **44** (3): 521 – 526.

Xia, X., Luo, J., and Yu, R., (2008). "Epidemiology of HCV infection among injection drug users in China: systematic review and meta-analysis". Public health ***122.***(10):990-1003.

Yu, M.L., Chuang, W.L., (March 2009). "Treatment of Chronic Hepatitis C in Asia: When East meets West." *J. Gastroenterol Hepatol* **24** (3): 336 – 45.

Zignego, A.L., Ferri, C., and Pileri, S.A., (2007). "Extragepatic manifestation of Hepatitis C virus infection; a general overview and guidelines for a clinical approach". *Digestive and Liver Disease* **39** (1); 2-17.

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