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Virulence Factors and Pathogenic Mechanisms of Hepatitis Viruses Versus Host Innate Immunity

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Abstract
The liver fulfils key functions in metabolism for proteins, carbohydrates, and lipids and for elimination of toxic waste products via bile. However, certain conditions can cause the inflammation of the liver such as use of alcohol, some certain medical conditions, toxins and medications, inflammation of the liver is most often caused by a virus. Meanwhile, viral hepatitis is caused by any of the five hepatotropic viruses, i.e hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). These viruses belongs to different families which include; Hepatitis A is caused by infection with hepatitis A virus (HAV), a non-enveloped RNA virus that is classified as a picornavirus and was first discovered in the 1973, Hepatitis B virus (HBV), is a member of the family Hepadnaviridae, it was discover in the 1960s, hepatitis C is an infectious disease caused by the hepatitis C virus (HCV), which is an RNA virus of the family Flaviviridae, and was discovered in the year 1989, The smallest virus known to infect humans is hepatitis delta virus (HDV), Hepatitis delta virus was discovered by Rizzetto in 1977 and was initially described as new antigen detectable in patients with HBV-associated chronic liver disease. HEV is a single-stranded, nonenveloped RNA virus and is the only virus within the family Hepeviridae, it was first recognised in the year 1980. These viruses have different virulence factors which enable them to replicate and disseminate within a host in part by subverting or eluding host defences. Furthermore, just as they have different virulence factors, they vary greatly in terms of pathogenic mechanism as well as host immunity evasion mechanisms. The immune systems interact with these viruses upon entry into the cells. The innate immune system serves as the initial immune defence against foreign and dangerous materials such as viruses. In conclusion, all used injections should be properly managed and disposed. Thus, bodily fluid samples as well as faecal materials should be regarded as highly infectious until otherwise proved to be safe. It is recommended that hepatitis status need to be determined thorough outreach screening exercise for individuals living in endemic areas to avoid transmission and any further liver complications. However, more research need to be carried out on the treatment of hepatitis viral disease as well as vaccine for Hepatitis C virus(HCV). In addition, blood for transfusion should be screened for hepatitis viruses prior to infusion. Finally, health education need to be done to help avoid the use of one needle among multiple drug users.

Keywords: Hepatitis virus, Virulence factors, immune system, Pathogenic mechanism

INTRODUCTION

Liver is one of the important organ in the body that plays vital role such as blood filtration, nutrients processing as well as fight against infections, the function of the liver is impaired when its inflamed (Center for Disease Control, 2020). The liver fulfils key functions in metabolism for proteins, carbohydrates, and lipids and for elimination of toxic waste products via bile. These functions are facilitated by the hepatic (micro)anatomy (Knolle and Thimme, 2014). Delivery of blood from the gastrointestinal tract, enriched in nutrients and bacterial degradation products, via the portal vein and arterial blood supply fuel large amounts of blood continuously to the liver (Knolle and Thimme, 2014). Certain conditions can cause the inflammation of the liver such as use of alcohol, some certain medical conditions, toxins and medications, inflammation of the liver is most often caused by a virus (CDC, 2020). Hepatitis can be caused by toxins, certain drugs, heavy alcohol use, infections by bacteria and viruses (CDC, 2012). The liver, which is made up of approximately 80% hepatocytes, is often considered a secondary lymphoid organ due to the amount of flowing through, infiltration, and resident immune cells (Faure and Durantel, 2017).

Hepatitis is an inflammation of the liver caused by certain viruses and other factors, such as alcohol abuse, some medications and trauma (CDC, 2020). The disease is an international public health challenge, comparable to other major communicable diseases, including HIV, tuberculosis and malaria and a global public health problem affecting millions of people every year, causing disabilities and deaths (WHO, 2016). Viral hepatitis refers to infections that affect the liver and are caused by viruses (NIH, 2013). Viral hepatitis, caused by any of the five hepatotropic viruses, i.e hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV), represents a major health problem worldwide (WHO, 2020). These viruses enter the host by one of the two major routes, enteral or parenteral (Kumar *et al*., 2010).

The disease described as “jaundice” in ancient Greek, Roman, and Chinese literature probably was viral hepatitis (Nainan *et al.*, 2006). Since the development of jaundice is a characteristic feature of liver disease, a correct diagnosis can only be made by testing patients’ sera for the presence of specific antiviral antigens or antibodies (WHO, 2002). A viral aetiology was postulated as the cause of certain forms of jaundice as early as at 1912, and hence the term“infectious hepatitis” was used because the disease often occurred in epidemics (Nainan *et al.*, 2006).

Virulence factors enable an organism to replicate and disseminate within a host in part by subverting or eluding host defences (Cross, 2009). The ability of an organism to adhere to host cells is a necessary condition allowing pathogens to colonize its host’s body (Sarowska *et al*., 2019). Microbial virulence factors encompass a wide range of molecules produced by pathogenic microorganisms, enhancing their ability to evade their host defences and cause disease (Leit, 2020). Pathogenic organisms invade and multiply in certain tissues and organs in the body. This phenomenon is referred to as tissue tropism and involves specific interaction with the target receptors and the surface of a particular tissue (Sarowska *et al*., 2019). This broad definition comprises secreted products such as toxins, enzymes, exopolysaccharides, as well as cell surface structures such as capsules, lipopolysaccharides, glyco and lipoproteins (Leit, 2020).

The immune function has been conceptually divided into innate and adaptive immunity. Innate immunity represents a rapid and stereotyped response to a large but limited number of stimuli (Cruvinel *et al*. 2010). It is represented by physical, chemical, and biological barriers, specialized cells and soluble molecules, present in all individuals, irrespective of previous contact with offending agents or immunogens, and does not change qualitatively or quantitatively after contact (Cruvinel *et al*., 2010).The innate immune system serves as the initial immune defence against foreign and dangerous material (Turvey and Broide, 2010). Innate immune cells, as well as nonparenchymal/non-professional cells endowed with innate functions, liver sinusoidal endothelial cells (LSEC), hepatic stellate cells (HSC), are particularly enriched in this solid organ called the liver (Faure and Durantel, 2017). The liver has unique immune regulatory functions that promote the induction of tolerance rather than responses to antigens encountered locally. These functions are mediated by local expression of co-inhibitory receptors and immunosuppressive mediators that help prevent over whelming tissue damage (Knolle and Thimme, 2014). The innate immune system uses a limited number of pattern recognition receptors (PRRs) to recognize pathogen associated molecular patterns (PAMPS) (Dranoff, 2004). Because the host does not produce PAMPs, the innate immune system is able to discriminate between self and nonself (Dranoff, 2004).

The Hepatitis viruses

Viral hepatitis, caused by any of the five hepatotropic viruses, i.e hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV),which represents a major health problem worldwide (WHO, 2020). These viruses enter the host by one of the two major routes, enteral or parenteral (Kumar *et al*., 2010). The disease described as "jaundice" in ancient Greek, Roman, and Chinese literature probably was viral hepatitis (Nainan *et al.*, 2006). Since the development of jaundice is a characteristic feature of liver disease, a correct diagnosis can only be made by testing patients' sera for the presence of specific antiviral antigens or antibodies (WHO, 2002). A viral aetiology was postulated as the cause of certain forms of jaundice as early as at 1912, and the term "infectious hepatitis" was used because the disease often occurred in epidemics (Nainan *et al.*, 2006). Viral hepatitis refers to infections that affect the liver and are caused by viruses (NIH, 2013).

The term Hepatitis A, was first introduced by Krugman *et al.,* in 1967, is now known to be caused by infection with hepatitis A virus (HAV), one of the five viruses, each belonging to a different family, whose primary site of replication is the liver (Nainan *et al.*, 2006). The HAV and HEV are enterally transmitted and cause an acute, self-limited infection, with complete resolution, except in rare situations in which fulminant disease with high mortality is observed (Kumar *et al*., 2010). Hepatitis A and hepatitis B (infectious and serum hepatitis, respectively) are considered separate diseases and both can be diagnosed by a specific serological test (NIH, 2013). Hepatitis C and E comprise a third category, each a distinct type, with Hepatitis C parenterally transmitted, and hepatitis E enterically transmitted (NIH, 2013).

The HBV, HDV and HCV are parenterally transmitted, cause acute infection with a high propensity to become chronic with long term sequelae such as cirrhosis and hepatocellular carcinoma (Kumar *et al*., 2010). Hepatitis D, or delta hepatitis, is another distinct virus that is dependent upon hepatitis B infection and this form of hepatitis may occur as a super-infection in a hepatitis B carrier or as a co-infection in an individual with acute hepatitis B (NIH, 2013).

Despite significant overlap in the clinical manifestations caused by them, the hepatitis viruses differ widely in their morphology, genomic organization, taxonomic classification and modes of replication (Kumar *et al*., 2010).

Hepatitis A virus (HAV)

Hepatitis A is an ancient disease that has likely afflicted mankind since humans first began to live in groups large enough to sustain transmission of the causative agent of hepatitis A virus (HAV) (Lemon *et al*., 2018). The virus has icosahedral symmetry contains a single stranded positive sense RNA of approximately 7500 nucleotides, he further described HAV as non-enveloped RNA virus 27 to 32 nm diameter in size, with an icosahedral symmetry, which belongs to the genus Hepatovirus of the Picornaviridae family (Nainan *et al*., 2006). Its single stranded, positive sense RNA genome is approximately 7.5 kb in length, with a lengthy 50 untranslated RNA (UTR) segment covalently linked to a small virally encoded protein, VPg (or 3B), at its 50 terminus (Lemon *et al*., 2018).

Hepatitis A is caused by infection with hepatitis A virus (HAV), a non-enveloped RNA virus that is classified as a picornavirus (Megan *et al.*, 1995). HAV was first identified by immune electron microscopy in 1973 and initially replicated in mammalian cell culture in 1979 (Megan *et al.*, 1995). Hepatitis A, formerly known as infectious hepatitis, is caused by the hepatitis A virus (IOCI, 2008). Hepatitis A is caused by the hepatitis A virus (HAV) (CDC, 2020). Unlike other members of the family, HAV requires a long adaptation period to grow in cell culture, replicates slowly, and rarely produce a cytopathic effect (Nainan *et al.*, 2006). HAV is stable in the environment for at least 1 month and is more resistant to heating and chlorine inactivation than is poliovirus(Nainan *et al.*, 2006).

The virus can be carried on the hands of an infected person who does not wash his or her hands thoroughly after using the toilet (IOCI, 2008). It enters through the mouth, multiplies in the body and is passed in the stool (IOCI, 2008). Hepatitis caused by hepatitis A virus (HAV) is a common disease affecting humans and has a high incidence throughout the world (Wang et al., 1996). The disease is rarely fatal, and most people recover in a few weeks without any complications (Nainan *et al*., 2006). Infants and young children tend to have very mild or no symptoms and are less likely to develop jaundice than are older children and adults (Nainan *et al*., 2006).

Hepatitis B virus (HBV)

Hepatitis B is a serious and common infectious disease of the liver, affecting millions of people throughout the world (WHO, 2002). Hepatitis B virus (HBV) infection is one of the most prevalent public health problems worldwide (especially in developing countries) (Gholamreza *et al*., 2007). Chronic infectionwith hepatitis B virus (HBV) is the main cause of liver cirrhosis and hepatocellular carcinoma (HCC)worldwide (Attia and Zhou, 2020). Hepatitis B has also been called type B hepatitis, serum hepatitis, homologous serum jaundice (WHO, 2002). Hepatitis B virus (HBV), a member of the family Hepadnaviridae, is a hepatotropic non-cytopathic DNA virus that despite the presence of an effective prophylactic vaccine is estimated to infect 300 million people, with a particularly high prevalence in Asia and Africa (Bertoletti and Gehring, 2006). The hepatitis B virus, a hepadnavirus, is a 42 nm partially double stranded DNA virus, composed of a 27 nm nucleocapsid core (HBcAg), surrounded by

an outer lipoprotein coat (also called envelope) containing the surface antigen (HBsAg) (WHO, 2002).

Hepatitis B is caused by the hepatitis B virus (HBV), an enveloped virus containing a partially double stranded, circular DNA genome, and classified within the family hepadnavirus (WHO, 2002). HBV is a member of the hepadnavirus family (Attia and Zhou, 2020). Hepatitis B virus (HBV) is a small hepatotropic, non-cytopathic DNA virus infecting humans and chimpanzees (Suslov *et al*., 2018). On primary infection, HBV spreads throughout the liver infecting up to 100% of hepatocytes and producing very high virus titers (up to w109 - 1010 particles per mL of serum) until after 6 to 10 weeks the adaptive immune response takes control over the virus, which happens in approximately 90% of immunocompetent adults (Suslov *et al*., 2018).

Hepatitis B virus (HBV) is a blood borne virus that infects the liver (Mark, 2018). Out of the many viral causes of human disease, few are of greater global importance than hepatitis B virus (Janssen and Feld, 2015). Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the most common causes of liver disease worldwide (Rehermann and Nascimbeni, 2005). Out of the many viral causes of human hepatitis few are of greater global importance than hepatitis B virus (HBV)(WHO, 2002). The virus interferes with the functions of the liver while replicating in hepatocytes (WHO, 2002). The immune system is then activated to produce a specific reaction to combat and possibly eradicate the infectious agent (WHO, 2002). As a consequence of pathological damage, the liver becomes inflamed (WHO, 2002). Both viruses can be transmitted parenterally, sexually and perinatally, with perinatal and sexual transmission being more common for HBV than for HCV (Rehermann and Nascimbeni, 2005). Until the discovery of the virus in the 1960s, it was transmitted sexually and by transfusion of contaminated blood and blood fractions (Mark, 2018).

Hepatitis C Virus (HCV)

Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV), which is an RNA virus of the family Flaviviridae (Buti and Razavi, 2017). HCV is a small, enveloped virus, a member of the Flaviviridiae family and the lone example of the genus Hepacivirus (Kumar *et al.*, 2010). The genome consists of a single stranded positive sense RNA molecule approximately 9.6 kb long encoding a large ORF, which is flanked by highly structured 5′ and 3′ untranslated regions (UTR) (Kumar *et al.*, 2010). The hepatitis C virus is an RNA virus that belongs to the family flaviviridae (CDC, 2012). The hepatitis C virus is an enveloped, positive-strand RNA virus, approximately 50nm in diameter (Mizukoshi and Rehermann, 2014). HCV is a member of the Flaviviridae family and the genus Hepacivirus, which also includes GB virus B and the recently identified non-primate, rodent and bat hepaci viruses (Buti and Razavi, 2017).

Since its discovery in 1989, hepatitis C virus (HCV) is estimated to have infected almost 200 million people, representing almost 3 % of world population (Kumar *et al*., 2010). Since the discovery of the virus in 1989, an intense interplay between basic, translational and clinical research has led to continuous progress in diagnostic tools and management strategies (Buti and Razavi, 2017). The hepatitis C virus (HCV) is a major cause of hepatitis (acute and chronic) and cirrhosis the world over (NIH, 2013). According to the Centre for Disease Control and Prevention, 21% of all acute viral hepatitis in the United States may be attributed to hepatitis C viral infection (NIH, 2013). Hepatitis C is a contagious liver disease caused by the Hepatitis

C virus (HCV) which is found in the blood of persons who have the disease (CDC, 2012). Hepatitis C is caused by HCV and is recognized as one of the leading causes of chronic liver disease associated with end stage cirrhosis and liver cancer (Khudyakov, 2012). Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the most common causes of liver disease worldwide (Rehermann and Nascimbeni, 2005).

Chronic hepatitis C is the most common cause of chronic liver disease and cirrhosis, and the most common indication for liver transplantation in the United States (U.S.), Australia, and most of Europe (CDC, 2012). Hepatitis C virus (HCV) is a parenterally transmitted RNA virus that causes chronic hepatitis and liver disease (Mizukoshi and Rehermann, 2014). In contrast to infections with other hepatitis viruses, the onset of HCV infection is clinically in-apparent in the majority of cases, and the diagnosis of hepatitis C is therefore typically made only after persistent infection is established (Mizukoshi and Rehermann, 2014). HCV replicates in the cytoplasm of hepatocytes, but is not directly cytopathic (CDC, 2012).

Hepatitis D Virus (HDV)

The smallest virus known to infect humans, hepatitis delta virus (HDV), is increasingly again becoming a cause of fulminant hepatitis or a more rapid progression of liver disease in the setting of chronic hepatitis B virus (HBV) infection (Abbas and Afzal, 2013). HDV is a defective satellite RNA virus which requires the helper function of HBV for its replication and assembly of new virions (Abbas and Afzal, 2013). In 1977, Mario Rizzetto and colleagues described a novel antigen in the nucleus of hepatocytes derived from patients infected with HBV (Wedemeyer and Manns, 2010). Hepatitis delta virus was discovered by Rizzetto in 1977 and was initially described as new antigen detectable in patients with HBV associated chronic liver disease (Margolis and Hadler, 2016). HDV is a small, spherical virus with a diameter of about 36nm. The viral genome is a circular, single-stranded, negative sense RNA molecule with an internal core delta antigen surrounded by an envelope derived from HBV surface proteins (Abbas and Afzal, 2013). The HDV RNA forms a rod shaped tertiary structure and encodes the delta antigen, which has two subspecies of slightly different length, the shorter of which is required for HDV replication and the latter for HDV packaging into viral particles (Margolis and Hadler, 2016).

The HDV virion is a large particle, approximately 36nm, and contains HDV RNA and hepatitis delta antigen (HDAg) (Wedemeyer & Manns, 2010). Unlike most RNA viruses, HDV does not encode its own replicase or RNA dependant RNA polymerase to replicate its genome (Abbas & Afzal, 2013). Rather, it makes use of cellular RNA polymerases which are DNA-dependant RNA polymerases (Abbas and Afzal, 2013). Since HDV genomic RNA has negative or antimessenger polarity, during replication three different forms of RNA are being made: circular genomic RNA, circular complementary antigenomic RNA and a linear antigenomic RNA through a circle rolling mechanism (Abbas and Afzal, 2013).

HDV is a satellite RNA virus that depends on HBV for propagation (Stockdale *et al*., 2020). It uses the HBsAg as a viral envelope and shares the same hepatocyte receptor for viral entry (Stockdale *et al*., 2020). HDV is among the smallest of viruses capable of causing human disease, yet HBV co-infection with HDV is the most severe form of viral hepatitis (Stockdale *et al*., 2020). Like other hepatotropic viruses, hepatitis D virus (HDV) also causes liver inflammation and produces symptoms similar to the other acute viral hepatitis diseases, just

probably more severe (Kumar *et al*., 2010). However, it is considered to be a subviral satellite because it can propagate only in individuals who are HBsAg positive or who have evidence of recent HBV infection (Kumar *et al.*, 2010).

Hepatitis E Virus (HEV)

Hepatitis E virus (HEV), the etiological agent of hepatitis E (HE), was described for the first time using electron microscopy in 1983 as a spherical viral particle being 27 to 30 nm in size (Vasickova *et al*., 2007). Hepatitis E was first recognized during an epidemic of hepatitis, which occurred in Kashmir valley in 1978 (Khuroo and Khuroo, 2004). The disease caused by HEV was first recognized as a widespread occurrence of non A, non B hepatitis in 1980 in India (Fayer *et al.,* 2009). HEV is a single-stranded, nonenveloped RNA virus and is the only virus within the genus Hepevirus and the family Hepeviridae (Manns, 2012). HEV particles are small, non-enveloped, 32-34 nm in diameter, with spikes and indentations on the surface (Khuroo and Khuroo, 2004).

HEV is an enterically transmitted human pathogen with worldwide distribution, the virus belongs to a newly described family of viruses that are small, single-stranded, positive-sense, non-enveloped RNA viruses originally placed in the Calicivirus family based on their structure and size (30 nm) (Fayer *et al.,* 2009). Hepatitis E has primarily been reported from countries of the developing world where the diagnostic capabilities to differentiate this disease from hepatitis A are limited (Margolis and Hadler, 2016). Hepatitis E is essentially the same disease as hepatitis A, with similar elevated liver enzyme levels. Hepatitis E should be considered if hepatitis A has been ruled out, particularly in outbreaks of waterborne hepatitis in developing countries or with patients that have recently travel to endemic areas (Fayer *et al*,. 2009).

VIRULENCE FACTORS OF HEPATITIS VIRUSES

Virulence factors of Hepatitis A virus

The virus has VP1 and VP3**, t**hese capsid proteins form a single, dominant antigenic epitope on the viral surface, which elicite a neutralising antibody response (Omana *et al*., 2006). These epitopes are highly conformational and thus, help them to evade the immune system (Omana *et al*., 2006). HAV Protease**,**the mature HAV protease, 3Cpro, also cleaves NF-kappa-B Essential Modulator (NEMO) or (IKBKG), a bridging adaptor required for NF-B activation and IFNb expression (Lemon *et al.*, 2018).3Cpro precursors, 3ABC and 3CD, to proteolytically cleave and functionally eliminate MAVS and TRIF (TICAM1), which are key signalling molecules involved in the induction of interferon responses (Lemon *et al.*, 2018).

Virulence factors of Hepatitis B virus

Reverse transcriptase**.** Sequestration and reverse transcription of pregenomic HBV RNA in immature nucleocapsids may block the induction of innate immunity (Mark, 2018). The fact that the pregenomic RNA and the reverse transcribed viral DNA product are sequestered within a nucleocapsid means that they are not readily detected by pattern recognition receptors, (e.g., toll-like receptors, retinoic acid inducible gene 1 (RIG-1), and mitochondrial anti-viral signaling (MAVS) that play role triggering innate immunity (Mark, 2018)**.** HBV Polymerase**,**HBV polymerase inhibits RIG-1 and nuclear factor kappa B (NF-κB) induction of

IFNβ, suggesting that the polymerase could block innate signaling, thereby contributing to virus persistence (Mark, 2018).

HBV core protein**,** HBV core protein interferes with IFN-β expression through binding to the IFN-β promoter as a transacting silencer (Attia and Zhou, 2020).HBeAg**,** HBeAg appears to be a T cell tolerogen that down-regulates immune responses against HBcAg (Mark, 2018). HBeAg may also stimulate the appearance of regulatory dendritic cells, which would also suppress virus specific immunity and promote virus persistence by up-regulating the expression of suppressor of cytokine signaling 2 (SOCS2), which in turn represses IFN signaling, thereby blunting innate anti-viral responses and promoting virus persistence (Mark, 2018)**.** HBx appears to block IFN expression and signaling, suggesting that both innate and adaptive immunity could be compromised, thereby permitting virus persistence (Mark, 2018).Hepatitis B surface antigen (HBsAg)**,**these subviral particles, which are produced at concentrations several logs above that of infectious virus particles, absorb neutralizing antibody and trigger immunological tolerance, both of which promote virus persistence in the blood (Mark, 2018).

Virulence factors of Hepatitis C virus

E2, NS2, P7, NS5A and NS5B proteins are known to interfere with IFN contributes to the viral resistance(Khudyakov, 2012). NS3, E2, NS3, and NS5A, NS3 has been shown to prevent the phosphorylation, dimerization, nuclear translocation and therefore, triggers the trans-activating function of IRF-3 (Guidotti and Chisari, 2006). The HCV NS3/4A protein can efficiently cleave and inactivate two host signalling pathways that react to HCV pathogen associated molecular patterns to induce the IFN pathway. Nevertheless, IFN-stimulated genes are induced during acute HCV infection, but this response is not very effective at clearing the virus (Buti and Razavi, 2017).

Although activated IRF-1 and IRF-3 are both known to induce IFN-β gene expression and stimulate expression of genes downstream of IFN-β, in view of the ability of E2, NS3, and NS5A to inhibit the activation of IFN-regulated genes one would not expect IFN-regulated genes to be strongly induced in the liver during HCV infection (Guidotti and Chisari, 2006). Hepatitis C protease, NS3/4A. Mitochondrial Antiviral Signalling Protein (MAVS) and TRIF (TICAM1) are key signalling molecules involved in the induction of interferon responses. Interestingly, these same signalling proteins are targeted by the hepatitis C protease, NS3/4A (Lemon *et al*., 2018).

The E1 envelope glycoprotein is believed to be the fusogen (the glycoprotein that facilitates cell fusion (Buti and Razavi, 2017). NS3/4A protease, the apparent resistance of HCV to these early innate defence mechanisms has been ascribed to the capacity of the HCV NS3/4A protease to block signalling from toll-like receptor 3 (TLR-3) and a recently discovered dsRNA binding protein (RIG-I) that triggers IRF3 activation and IFN-β gene expression (Guidotti and Chisari, 2006). For example, the E2and NS5Aproteins of HCV have been shown to bind to the kinase domain of dsRNA-dependent protein kinase (PKR) and inhibit interferon regulatory factor (IRF)-1 phosphorylation (Guidotti and Chisari, 2006).

However, it is important to note a significant concordance in genetic factors affecting HCV clearance, severity of liver disease and response to IFN based therapy, which suggests a strong

link between virulence and IFN resistance (Khudyakov, 2012). HCV variants that resist IFN treatment seem to interfere efficiently with IFN pathways and reduce its antiproliferative activity thus, potentially contributing to carcinogenesis (Khudyakov, 2012). Since chronic HCV infection is associated with development of liver disease and HCC, resistance to IFN is effectively an essential determinant of virulence (Khudyakov, 2012).

Virulence factors of Hepatitis D virus

L-HDAg and HDAg-S;HDAg-S is produced during the early stages of infection and is essential for viral replication, HDAg-L is produced during infection and functions as an inhibitor of viral replication but facilitator of viral assembly (Kumar *et al*., 2010). L-HDAg has been shown to stimulate transforming growth factor-β (TGF-β) and c-Jun induced signaling cascades which in turn may induce epithelial-mesenchymal transition and fibrogenesis (Abbas and Afzal, 2013). L-HDAg can also activate the TGF-β pathway, probably via the Smad III protein, which could promote HCC development. HBV can also upregulate TGF-β via the HBx protein, which could be the mechanism by which HDV enhances HBV related oncogenesis. This effect could be synergistic with that of the HBx protein, which also activates these two signalling cascades (Kumar *et al*., 2010). Another proposed mechanism involves nuclear factor kappa B (NF-kB), a transcription factor with crucial roles in inflammation, immunity, cell proliferation and apoptosis, and HCC development (Kumar *et al*., 2010).

Virulence factors of Hepatitis E virus

No specific virulence factors have been associated with any human or animal strains of HEV, although different genotype of the virus differs pathologically, genotypes 3 and 4 generally appear less virulent than genotypes 1 and 2 (Fayer *et al.*, 2009).

Host innate immunity against the hepatitis viruses

The first line of defence against any viral agent is antigen nonspecific, and the earliest response is probably elicited by virus-infected cells (CDC, 2012). One of the earliest and common viral products in infected cells is double stranded RNA, and most cells respond with synthesis of type I interferons, i.e., IFNα and, which are cytokines characteristic of the innate immune response. Type I IFN can inhibit the replication of many viruses (CDC, 2012).

Most viruses activate the innate immune system in the cells they infect, because they bring along, or generate so-called pathogen-associated molecular patterns (PAMPs) (typically viral genomes or replication intermediates) that the host cell recognizes as foreign. Cells detect those PAMPs using pattern recognition receptors (PRRs), such as cytoplasmic retinoic acid-inducible gene I (RIG-I)-like receptors (RLR) that specifically detect 5′-triphosphate-containing RNA and double-stranded RNA (dsRNA) in the cytoplasm of infected cells, and endosomal toll-like receptors (TLRs) that detect incoming dsRNA (TLR3), single-stranded RNA (ssRNA) (TLR7/8), or CpG motif-containing un-methylated DNA (TLR9) (Suslov *et al*., 2018). The activation of these sensory pathways results in production of interferons (IFNs) and expression of interferon-stimulated genes (ISGs) that limit viral replication and spread (Suslov *et al*., 2018).

According to Leikina *et al*. (2005), The innate immunity has a number of roles in recognition and clearance of viral infgection. The innate immune system, contributes greatly to immune

surveillance in organ system and in the circulation, directly neutralise infections as well as trigger inflamation, opsonizing pathogens and modulating adaptive immunity (Iwasaki and Medzhitov, 2010). Complex interplay takes place between cellular components of the innate immunity , these cells include; monocytes, dendritic cells, Natural kiler cells (Iwasaki and Medzhitov, 2010). Meanwhile, these cells detect pathogens and contribute to their clearance by activating T and B cells and by directing degrading pathogens (Fitzgerald and Feng, 2007). Thus, the role of the innate cells is intimately related with recognition by humoral innate immune proteins, a diverse group of proteins thatr act as pattern recognition receptors (PRRs) and these proteins recognise pathogen Associated Molecular Pattern (PAMPs) on the infecting virus particles, or presented on the surface of infected cells (Iwasaki and Medzhitov, 2010). These PRRs may include; Pentraxins, and deffence collagens such as C-type lectins and ficolins (Iwasaki and Medzhitov, 2010).

Despite this intrinsic immune tolerance, the liver is well equipped to mount a potent antimicrobial response, and successful pathogens have also evolved strategies to either passively or actively evade innate and adaptive immune responses in order to persist (Faure and Durantel, 2017). Viral infection triggers the induction of type-I interferons (e.g IFN-α and IFN-β) and other proinflammatory cytokines through two distinct signaling pathways (Attia and Zhou, 2020). Most viruses are detected at early stages of cell infection and induce an innate immune response mediated by production of interferons (IFNs) (Suslov *et al*., 2018). Innate immunity generally plays a role immediately after infection to limit the spread of the pathogen and initiate efficient development of an adaptive immune response (Bertoletti and Gehring, 2006). Innate host responses during the early phases of viral infections are mainly characterized by the production of type 1 interferon (IFN) a/b cytokines and the activation of natural killer (NK) cells, production of type 1 IFNs can be triggered directly by virus replication through cellular mechanisms that detect the presence of viral RNA or DNA (Bertoletti and Gehring, 2006).

Furthermore, elements of the complement cascade contribute greatly in the recognition of pathogens both directly and as part of immune complexes consisting of immunoglobins cross-linked by viral antigens on the surface of virion or infected cells (Iwasaki and Medzhitov, 2010). However, the complement system and associated pathways also have functional effector properties, activating cascade of proteins responsible for opsonization and lysis of enveloped virions and infected cells, the humoral innate immune proteins circulate in the bloodstream, and function both in the serum and in tissue (Iwasaki and Medzhitov, 2010). Barrionuevo *et al*., (2007), stated that the innate immune system is highly integrated with adaptive immunity. Soluble innate molecules cam modulate antigen presentation, directing the specficity of T cells and antibodies. In turn, antibodies can trigger and modulate innate antiviral effector mechanisms, contributing to enhance antigen presentation (Bayry *et al*., 2005).

Humoral innate immune factors are produced by different types of cells including monocytes, lymphocytes and hepatocytes (Bayry *et al*., 2005). Generally, hepatocytes are the primary source of the complement components, manose binding lectin and the ficolins such as the L-ficolins and H-ficolins (Bayry *et al*., 2005). High concentration of these proteins localise and may accumulate in the liver and as such may have important anti-viral hepatitis activity at the site of infection in the liver (Akaiwa *et al*., 1999). The family of ficolins share great structural similarity to the collectins and play a similar functions in the innate immunity (Akaiwa *et al*.,

1999). Three human ficolins have beeen identified; M- ficolins is produced by macrophages in response to pro-inflamatory cytokines, L-ficolins and H-ficolins are both express by hepatocytes (Akaiwa *et al.*, 1999).

CELLS OF THE INNATE IMMUNE SYSTEM

Dendritic cells

These cells are specialised in the capturing and presenting antigens to lymphocytes and they are considered a bridge between innate and adaptive immunity because they are attracted and triggered by element of the innate response and hence permit T-lymphocyte sensiblization of the adaptive immune response (Wilson *et al.*, 2010). Dendritic cells (DCs) are found in peripheral tissues such as skin, liver and intestine where they engulf antigens and become activated and move to regional lymph nodes, in which they process and present protein antigen or lipid to to T- lymphocytes (Wilson *et al*., 2010). Immature dendrtic cells are highly efficient in engulfing antigens, while mature DCs arebvery efficeint in presenting antigens (Banchereau *et al*., 2000). Meanwhile, the engulfed antigens are processed within the cell and presented on its surface, bound to MHC molecule (Banchereau *et al*., 2000).

Neutrophils

Wilson *et al*., (2010), found that the neutrophils are the most abundant leukocytes in peripheral blood, with a vital role in the early stages of inflmatory reaction and sensitive to chemotactic agents such as cleavage products of complements fraction (C3a and C3b) and substances and substances release by mast cells and basophils. They are among the first cells to move from vessels to tissues attracted by chemokins such as IL-8 and are triggered by various stimuli such as bacteria products, complement proteins (C5a), immune complex (IC), chemokines and cytokines.

Macrophages

Wilson *et al*., (2010), stated that monocytes constitute 3-8 % of circulating white blood cells and in connective tissue or parenchyma of organs, they give rise to macrophages amd myeloid dendritic cells. Monocyte and macrophages are effiecient phagocyte, capturing pathogens and cellular debris. Unlike neutropjhils, macrophages can remain in tissue for months and even years actig as true sentinels. Besides haing a role in innate immunity, macrophages process and present antigen through MHC molecules, hence stimulating the response mediated by TL4.

Natural killer cells

Natural killer cell originate in the bone marrow from a common progenito to TLs, it constitute about 5 to 20 % of blood mononuclear cells (Wilson *et al*., 2010). They are important line of nonspecific deffense, recognizing and lysing cells infected by viruses, bacteria, protozoa as well as tumor cells (Wilson *et al*., 2010). Another effector action of Nk cells is the destruction of cells coated with IgG through Fc receptors by a mechanism of body-dependent cellular cytotoxicity (ADCC) (Cererwenka and Lanier, 2001).

Mast Cells

These cells are derived from CD34 plus hematopoietic progenitors in the bone marrow and in general, the cells are not found in the circulation (Wilson *et al*., 2010). From bone marrow, the progenitors are move to peripheral tissue as immature cells and differentiate *in situ* according to the certain conditions of the microenvironment (Kitamura *et al.*, 1987). Mature mast cells are distributed strategically to the blood vessels, nerves and under the epithelium of the skin and mucous membrane, they particularly abundant in areas of environmental contact and play an important role in acute inflamatory reponse (Wilson *et al.*, 2010). The binding of pathogens especially viruses to TLRs 1, 2, 3, 4 and 6 and other specific receptors such as CD48, can activates mast cells, leading to mediators release, after stimuli, degranulation and release of preform mediators occur, followed by the release of newly formed mediators (Wilson *et al.*, 2010). The release of these mediators induces inflamatory cells migration (Neutrophils, and macrophages), increase vascular permeability, mucus secretion, increased gastrointestinal motility and bronchoconstriction, which are the signs and symptoms of alergy reaction (Metcalf, 2008).

The complement system

This is the family of more than twenty (20) plasma glycoproteins, synthesized in the liver, but also by macrophages and fibroblast (Wilson *et al.*, 2010). Each complement componentactivated acquire proteolytic activity to activate the next element in the complement cascade (Wilson *et al.*, 2010). In the process, there is the production of several mediators that alter vascular permeability and contribute to the development of inflamatory response (Wilson *et al.*, 2010). At the end there will be formation of membrane attact complex (MAC), which enhance osmotic lysis of target-cell, favouring the elimination of the infectious agent (Abbas and Lichtman, 2003).

PATHOGENIC MECHANISM OF HEPATITIS VIRUSES

Pathogenic mechanism of Hepatitis A Virus (HAV)

Following infection, HAV presumably replicates in the small intestine, from there it reaches the liver through portal circulation (Kumar *et al*., 2010). HAV replicates to high titters in the liver, with viremia and faecal shedding, suggesting that HAV may regulate host pathways for virus recognition and clearance (Kumar and Jameel, 2010). Innate immunity to limit the spread of viral infection is based primarily on interferon production by infected cells, during the incubation period, Plasmacytoid dendritic cells (pDCs), which typically produce large amounts of type 1 interferon in response to viral infections, respond robustly when placed in co-culture with HAV- infected cells or exposed to HAV (Lemon *et al*., 2018).HAV was shown to attenuate the interferon response by inhibiting the RIG-I-mediated signalling pathway, thus potentially evading innate immunity (Kumar and Jameel, 2010). This may be due to the ability of 3Cpro precursors, 3ABC and 3CD, to proteolytically cleave and functionally eliminate MAVS and TRIF (TICAM1), key signalling molecules involved in the induction of interferon responses (Lemon *et al*., 2018). Interestingly, these same signalling proteins are targeted by the hepatitis C protease, NS3/4A (Lemon *et al*., 2018). The mature HAV protease, 3Cpro, also cleaves NEMO (IKBKG), a bridging adaptor required for NF-jB activation and IFN-b expression (Lemon *et al*., 2018).

Pathogenic mechanism of Hepatitis B Virus (HBV)

HBV Infection and Host Innate Immunity, Innate immunity is the first line of defense against microbial pathogens, including viruses (Attia and Zhou, 2020). It is possible that this initial host response to HBV is primarily sustained by NK and NK-T cells (Bertoletti and Gehring, 2006). Although there is no direct evidence for the role of NK and NK-T cells during natural HBV infection, the possibility that the initial burst of IFN-c and the subsequent rapid inhibition of HBV could be mediated by these components of innate immunity (Bertoletti and Gehring, 2006).

HBV Recognition by Innate Sensors, the early and non-specific detection of pathogens generally occurs, at subcellular/molecular levels, via the recognition of Pathogen-Associated Molecular Patterns (PAMP) by innate immunity sensors, also called Pathogen Recognition Receptors (PRR) (Faure and Durantel, 2017). Amongst PRR, there are toll-like (TLR), Retinoic acid-Inducible Gene I (RIG)-like, nucleotide-binding oligomerization domain-containing protein (NOD)-like, C-type Lectin, and DNA-sensing receptors, which are differentially or ubiquitously expressed in various types of epithelial/endothelial cells, as well as professional and non-professional immune cells, upon interaction between a PRR and its cognate PAMP, various downstream signaling pathways are activated and sequentially involve (Faure and Durantel, 2017).

HBV seems to avoid the induction of strong innate immune responses during the first weeks of infection, but this does not affect the high recovery rate (Rehermann and Nascimbeni, 2005). IFN-α- and IFN-β-induced mechanisms inhibit the formation of new HBV capsids, destabilize existing capsids and degrade preformed HBV RNA (Rehermann and Nascimbeni, 2005). This antiviral effect is not mediated by typical IFN-induced proteins such as myxovirus resistance 1 (MX1), RNase L, IFN- inducible double-stranded-RNA-dependent protein kinase (PKR) or IFN-regulatory factor 1 (IRF1) and it seems to be proteasome dependent (Rehermann and Nascimbeni, 2005). In addition, downregulation of HBV replication can be mediated by IFN-γ that is produced by activated natural killer T (NKT) cells and T cells (Rehermann and Nascimbeni, 2005). Sequestration and reverse transcription of pregenomic HBV RNA in immature nucleocapsids may block the induction of innate immunity (Mark, 2018).Thus, activation of elements of innate immunity able to produce large quantities of IFN-c seems to be a factor that determines the subsequent efficient induction of adaptive immunity and ultimately the outcome of HBV infection (Bertoletti and Gehring, 2006). In addition, although HBV replication is exquisitely sensitive to inhibition by IFNs, HBx appears to block IFN expression and signaling, suggesting that both innate and adaptive immunity could be compromised, thereby permitting virus persistence (Mark, 2018)**.**

A further characteristic of HBV in relation to early host defence mechanisms resides in the lack of IFN-a and b production (Bertoletti and Gehring, 2006). HBV replication can be efficiently limited by a and b IFN (Bertoletti and Gehring, 2006). Nevertheless, it is interesting to note that the lack of early symptoms in HBV- infected patients such as fever and malaise, which are characteristic of other human viral infections, constitutes indirect evidence of the defective type I IFN production during the early phases of HBV infection (Bertoletti and Gehring, 2006). HBV might not induce an innate immune response because it is not detected by pattern recognition receptors or because HBV suppresses IFN production or signalling despite

detection by pattern recognition receptors) (Suslov *et al*., 2018). The activation of IFN-c, interleukin (IL)-2 and tumour necrosis factor (TNF)-a and intrahepatic recruitment of inflammatory cells is delayed until the logarithmic expansion of HBV (Bertoletti and Gehring, 2006).

Pathogenic mechanism of Hepatitis C virus (HCV)

HCV enters a susceptible host either directly, through transfusion of contaminated blood products or injection with contaminated needles, or, less efficiently, by crossing over an epithelial barrier, as exemplified by perinatal or sexual transmission (Mizukoshi and Rehermann, 2014). The virus reaches the liver via the hepatic artery or the portal vein and enters hepatocytes, its preferred site of replication (Mizukoshi and Rehermann, 2014). Viral attachment involves the two envelope glycoproteins, E1 and E2, apolipoproteins present at the surface of the lipoviroparticles and several cell surface molecules (Buti and Razavi, 2017). After attachment, HCV entry into cells results in clathrin mediated endocytosis, followed by fusion between viral and endosomal membranes, which leads to the release of the nucleocapsid into the cytoplasm (Buti and Razavi, 2017). The E1 envelope glycoprotein is believed to be the fusogen (the glycoprotein that facilitates cell fusion)(Buti and Razavi, 2017). Innate immune defences are triggered through host recognition of viral macromolecular motifs, known as the ‘pathogen associated molecular patterns (PAMP)’ (Kumar and Jameel, 2010). The RIG-I protein has been shown to bind HCV polyU/UC PAMP motif at the 3′UTR and trigger the hepatic immune response by signalling through activation of IRF3 to induce the expression of IFN α - β and interferon-stimulated genes (ISG) (Kumar and Jameel, 2010). Together, these limit the infection (Kumar and Jameel, 2010).

E1, E2 interacts with CD81 and scavenger receptor class B member 1, whereas claudin 1, occludin and possibly other molecules, such as claudin 6 or claudin 9, epidermal growth factor receptor or ephrin receptor type A2, are required for cell entry (Buti and Razavi, 2017). This multi-receptor complex mediates uptake and defines organ and species specificity (Buti and Razavi, 2017). The apparent resistance of HCV to these early innate defense mechanisms has been ascribed to the capacity of the HCV NS3/4A protease to block signaling from toll-like receptor-3 (TLR-3) and a recently discovered dsRNA binding protein (RIG-I) that triggers IRF-3 activation and IFN-β gene expression (Guidotti and Chisari, 2006).

In addition, several structural and non-structural proteins of HCV inhibit non over lapping functions of the innate immune response(Guidotti & Chisari, 2006). For example, the E2 and NS5A proteins of HCV have been shown to bind to the kinase domain of dsRNA-dependent protein kinase (PKR) and inhibit interferon regulatory factor (IRF)-1 phosphorylation (Guidotti and Chisari, 2006). In addition, NS3 has been shown to prevent the phosphorylation, dimerization, nuclear translocation and, therefore, the transactivating function of IRF-3 (Guidotti and Chisari, 2006). Although activated IRF-1 and IRF-3 are both known to induce IFN-β gene expression and stimulate expression of genes downstream of IFN-β, in view of the ability of E2, NS3, and NS5A to inhibit the activation of IFN-regulated genes one would not expect IFN-regulated genes to be strongly induced in the liver during HCV infection (Guidotti and Chisari, 2006).

Pathogenic mechanism of Hepatitis D virus (HDV)

Abbas and Afzal (2013), reported that following interactions between HBV and the innate immune system; IFN-α signalling by the virus infected cells to warn their neighbouring cells of a viral presence is a first line of defence of the host to eradicate viruses. IFN-α is induced by the double stranded RNA presented during viral replication. The IFNs thus produced, exert their effect by binding to α and β-IFN receptors on the cell surface, resulting in activation of the tyrosine kinases of the janus kinase (JAK) family which in turn phosphorylate tyrosine residues of the cytoplasmic transcription factors acting as signal transducer and activator of transcription (STAT). Activation of JAK/STAT signalling pathway stimulates the expression of IFN induced genes. The IFN-α-stimulated genes then code for the antiviral proteins, namely myxovirus resistance A, double stranded RNA (dsRNA) activated protein kinase and 2',5'oligoadenylate synthetase which, in turn, mount an antiviral response. L-HDAg has been shown to stimulate transforming growth factor-β (TGF-β) and c-Jun induced signaling cascades which in turn may induce epithelial-mesenchymal transition and fibrogenesis. The resultant activated nonspecific innate and specific acquired immune responses help combat the viral infection, but this is not the case in the setting of HDV infection.

Pathogenic mechanism of Hepatitis E virus (HEV)

The hepatitis E virus enters the body via the oral route, the site of primary replication is presumed to be in the intestinal canal(Khuroo *et al*., 2004). Hepatitis E virus HEV is not directly cytopathic and liver injury may be mediated by the host immune response (Kumar *et al*., 2010).The virus reaches the liver via portal vein. The liver appears to be the sole target of infection and once established viral replication occurs, leading to viral shedding in bile. The pathogenesis of hepatitis E may be a combination of direct cytotoxicity and immunologic mechanisms (Khuroo *et al*., 2004). cytotoxic lymphocytes have been found to infiltrate the liver tissue of infected animals, recent study suggests that natural killer (NK) cells might be involved in HEV pathogenesis, and there may be an inherent defect in T cell activation in HEV-infected persons (Kumar *et al*., 2010).

Control of Hepatitis virus infections

Vaccination is used as a method of control of hepatitis A (CDC, 2015). The hepatitis vaccine include an inactive form of the virus with life lasting antibodies that protect against the disease (WHO, 2015). The vaccine helps to trigger the natural immune system causing the body to make antibodies against the hepatitis A virus, the vaccination is usually done at the early age, at the age of one. Practice of good hygiene is also advisable as a form of control method (CDC, 2015).Vaccines for hepatitis B virus provide excellent protection against HBV infection (WHO, 2009). Vaccination consist of 3 doses of vaccine (shot) over the course of six months. The lifespan for protrection lasts twenty (20) years to life. The vaccine should be given for persons traveling to endemic countries (Yellow, 2008).HBV transmission can be prevented by screening of donated blood and plasma, by virus inactivation in plasma derived products and by implementation of infection control practices (Kumar and Jameel, 2010). However, the single most effective prevention measure is routine immunization for infants and high-risk individuals. Infants born to HBsAg carrier mothers can be protected against perinatal transmission by passive immunization (Kumar and Jameel, 2010).

As long as a prophylactic vaccine is not available, the HCV pandemic has to be controlled by treatment as prevention strategies, effective screening programmes and global access to treatment (Buti *et al*., 2017). Routine anti-HCV screening of blood donors (with or without surrogate marker testing) will substantially reduce the incidence of posttransfusion hepatitis C, routine anti-HCV screening of donors of organs, tissues, and semen is essential in the control of hepatitis C vrus disease (Margolis *et al*., 2016).There is no vaccine for hepatitis D(Kumar and Jameel, 2010). However, hepatitis D can be controlled base on the control of hepatitis B virus, as the former requires HBsAg for its propagation. In order to prevent HDV-HBV co-infection, the HBV vaccine or post exposure prophylaxis (Hepatitis B immunogloblin) can be used (Vijay *et al.*, 2010). It is equally important to educate the chronic HBV cariers about the transmission and risk factors of HDV. Direct contact with infected blood should be avoilded (Vijay *et al.*, 2010).

As hepatitis E is an ecologically determined disease, its control would depend upon improved sanitation, proper sewage disposal and supply of safe potable water. Mass education during and between outbreaks advising the public to follow proper hygienic precautions and to use boiled drinking water may be helpful (Khuroo *et al.*, 2004). Prevention is linked to proper hygiene, safe drinking water and proper sewage disposal, a recombinant vaccine against HEV has recently been tested in humans and was found to have good efficacy (Kumar and Jameel, 2010). Based on current understanding of HEV transmission indicates that effective prevention and control depend on ensuring a safe drinking water supply, adequate sanitation, and proper personal and environmental hygiene.

Conclusion

Liver is one of the important organ in the body that plays vital role such as blood filtration, nutrients processing as well as fight against infections, the function of the liver is impaired when its inflamed. The Inflammation of the liver is commonly referred to as hepatitis, which can be caused by different types of viruses ranging from hepatitis A, hepatitis B, hepatitis C, hepatitis D and hepatitis E. However, virulence factors enable an organism to replicate and disseminate within a host by subverting or eluding host defences. The ability of an organism to adhere to host cells is a necessary condition allowing hepatitis viruses to colonize their host's body. However,the innate immune system serves as the initial immune defence against foreign and dangerous material. Innate immune cells, as well as nonparenchymal/non-professional cells endowed with innate functions, liver sinusoidal endothelial cells (LSEC), hepatic stellate cells (HSC), are particularly enriched in this solid organ called the liver. All the five viruses causing hepatitis virus disease differs greatly in terms of virulence factors, pathogenic mechanism as well as host immunity evasion mechanisms.

Recommendations

All used injections should be properly managed and disposed. Thus,bodily fluid samples as well as faecal materials should be regarded as highly infectious until otherwise proved to be safe. Hepatitis status need to be determined thorough outreach screening exercise for individuals living in endemic areas to avoid transmission and any further complications in the liver. However, more research need to be carried out on the treatment of hepatitis viral disease as well as vaccine for Hepatitis C virus(HCV). Furthermore, blood for transfusion should be

screened for hepatitis viruses prior to infusion. Finally, health education need to be done to help avoid the use of one needle among multiple drug users.

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