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Insights Into Hepatitis Pathogenesis, Host Interactions And Genotypes

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Abstract

Hepatitis is a global public health challenge that affects millions of people worldwide. It is an inflammation of the liver that can be caused by various factors, including viral infections, alcohol consumption, and certain medications or toxins. Viral hepatitis is of particular concern as it can lead to severe liver damage and potential life-threatening complications.

The World Health Organization recognizes five main types of viral hepatitis: hepatitis A, B, C, D, and E. Every type has distinct modes of transmission, clinical manifestations, and long-term consequences.

To address this public health issue, the World Health Organization has developed comprehensive strategies and guidelines for the prevention, control, and elimination of viral hepatitis. These strategies focus on increasing awareness, improving access to testing and treatment, implementing vaccination programs, promoting safe injection practices, and reducing the burden of viral hepatitis-related liver diseases.

Efforts to combat hepatitis also involve strengthening health systems, fostering international collaboration, and advocating for policy changes to ensure equitable access to prevention and treatment services for all individuals, regardless of their socioeconomic status or geographic location**.**

Key words: Hepatitis, pathogenesis, genotypes, transmission

Introduction

Hepatitis A is a pathological acute inflammation of the liver caused by Hepatitis A virus (HAV). Before 1973, research done on viral Hepatitis has shown two distinct patterns of infection “Infectious Hepatitis” for the pattern that had symptoms, and “Serum Hepatitis” for the pattern that didn’t show any symptoms, but, by 1973, Multiple Scientists identified that the pattern that had symptoms was named “Hepatitis A” due to Australia Antigen being discovered. Hepatitis A virus is a Positive-sense RNA virus from the Herpavirus genus of the Picornaviridae family, with 4 different genotypes specified in humans. The Hepatitis A virus is a small non-enveloped (27 nm) particle in an icosahedral shape**.(1)**

Mode of Transmission

Hepatitis A virus is most likely to be transmitted via the Feco-oral route, either by contaminated food or water, or by poor sanitation and hygiene. Other causes include, living with an infected person. In areas endemic to the disease, Hepatitis A infection can happen during childhood**.(1)**

Pathogenesis & Host Interactions

The first step of the viral infection is to replicate inside the host. This is done by the infected liver releasing Enveloped Hepatitis A virus from the hepatocytes into the biliary system, where the bile salts cause the virus's envelope to be removed. The non-enveloped Hepatitis A virus is passed through the intestinal tract to be excreted in the stool where it is now infective**.(2)**

In a new case of Hepatitis A, fecal shedding of the virus and viremia occur and are followed by damage to the liver cells, which is revealed by elevation of the serum liver enzymes**.**

Extra-hepatic sites of Hepatitis A virus replication have been reported where the Hepatitis A antigen can be detected in the spleen, lymph nodes, and kidney of other primates. The antigen has also been detected in the tonsils and saliva of humans shortly after viremia, although it is extremely low**.**

After the virus entry and replication, it causes the immune system to infiltrate the liver by mononuclear inflammatory cells, thus causing degeneration of the liver cells. The Kupffer cells are then activated, and bile canaliculi disruption takes place. The mechanism of liver injury is not caused by the cytopathic effect of the virus, instead it is caused by the immune-mediated mechanisms including both innate and adaptive immune response to the virus, suggesting a role for T-cells, chemokines, and cytokines in the infected patients. T cells can be seen in the liver along with an increase in serum ALT levels, while the viral titers in stool and serum start to decrease, which suggest the significant role for T-cells in liver injury**.(2)**

Immune complex and reduced levels of serum complement also appear in Hepatitis A infection. These immune complexes contain C3 complement cleavage products, IgM, IgG antibodies, and HAV capsid proteins **.**

A recent study shows that a large number of antibody-secreting cells have specificities to antigens unrelated to Hepatitis A virus, a bone-marrow plasma cell-like phenotype, and mainly secretes IgM during Acute Hepatitis A infection. This suggests that pre-existing plasma cells are mobilized and released into the blood to secrete antigen-nonspecific IgM **.**

Different types of cytokines and chemokines play a role in immune-mediated host injury by their immunomodularity functions and effector. In infected patients, serum levels of chemokines and cytokines are increased including, Interleukin-6, 8, 18, and 22, Granzyme B and soluble Fas ligand, which are involved in T-cell cytotoxicity**.(2)**

In immune-mediated host injury, Regulatory T-cells can modulate effector T-cell Activity. These regulatory T-cells have been shown to have an effect on the regulation of liver injury, while their suppressive function can be inhibited by binding of the Hepatitis A virus to the TIM-1 expressed by the regulatory T-cells. It is important to note that if the number of the regulatory T-cell and their suppressive activity are increased, it would cause the serum ALT levels to decrease**.(1)**

Clinical Manifestations

Hepatitis A virus has an incubation period of about 2-4 weeks. The most commonly presenting symptoms are fever, jaundice, and malaise. Other common symptoms include nausea, weakness, fatigue, abdominal pain, arthralgias, vomiting, diarrhea, myalgias and anorexia**.**

About 10%-15% of patients have reported a relapsing infection course within 6-months of the original infection. The symptoms during the relapse are expected to be less severe than the initial infection. The spectrum of infections can range from asymptomatic patients without jaundice, to relapsing infection and/or acute liver failure, but it does not progress to chronic hepatitis**.(3)**

Investigations

Hepatitis A cannot be diagnosed by its symptoms only, but it must include laboratory diagnosis. These tests include an elevation of serum transaminase levels, direct and total bilirubin and alkaline phosphatase which remain elevated for only 2 or 3 months, they then return to normal levels. In cases of severe symptoms, other diagnostic measures include CBC, Prothrombin time, serum electrolytes, and glucose levels**.**

While the epidemiologic factors can help in suspecting a diagnosis, a serological test is required to confirm a diagnosis. IgM anti-hepatitis A antibodies usually become detectable 5 to 10 days before the onset of symptoms, and peak 1 month of infection, and remain detectable for more than 6 months. IgG anti-hepatitis A antibodies become detectable during the convalescent phase, and remain elevated throughout the patient's

lifetime, and it indicates protection against Hepatitis A. Unimmunized patients who test positive for IgM anti-hepatitis, but test negative for IgG anti-hepatitis indicate a past infection and recovery of Hepatitis A **.(3)**

Prevention

The main way to prevent Hepatitis A infection is by vaccination. An inactivated Hepatitis A antigen is injected into the body, to stimulate an infection and train the immune system to fight this antigen. There are 2 single-antigen vaccines (Vaqta and Harvix). There is also a vaccine called (Twinrix) which contains both Harvix vaccine and a Hepatitis B antigen. Vaccine effectiveness for Vaqta is reported to be 100% for only one dose, while the effectiveness of Harvix is reported to be 94% for 2 doses. Routine vaccination is recommended for children younger than 2 years, and in high-risk areas, and pregnant females. Health care worker, Plumbers, and sewer workers are not recommended to routinely take Hepatitis A vaccine**.**

If an unvaccinated person is exposed to an infected patient, or had contaminated food, or is planning to visit an area with a high risk of infection, they should receive an Immune globulin (Gama-stan) and the vaccine simultaneously. The Immune globulin (Gama-stan) should be preserved for patients who are contraindicated of the vaccine, or who are allergic to neomycin**.(4)**

Hepatitis B

Introduction

HBV belongs to the family of hepadnaviruses. The virus, measuring 42 nm in diameter, is enveloped and has an icosahedral nucleocapsid core that houses a partly double-stranded circular DNA genome **.**

Acute (short-lived, severe) or chronic (long-term) infections with hepatitis B virus are both possible. Hepatitis B increases the risk of developing liver cancer and cirrhosis, as well as the possibility of a chronic infection **.**

The genome consists of four genes that produce five proteins. The surface antigen (HBsAg), a protein found in the envelope, is critical for both immunization and laboratory diagnosis. There is a DNA-dependent DNA polymerase inside the core. The S gene encodes the surface antigen, the C gene encodes the core antigen and the e antigen, the P gene encodes the polymerase, and the X gene encodes the X protein **.(4)**

Mode of Transmission

Hepatitis B is primarily transmitted vertically (transplacental) or horizontally (via exposure to contaminated blood)**.**

In addition, exposure to contaminated blood and bodily fluids, including saliva and menstrual, vaginal, and seminal secretions, tattooing, piercing, and needle stick injuries can all transmit hepatitis B. Reusing contaminated syringes, needles, or sharp items among injecting drug users in public, healthcare facilities, or other settings can also spread the infection. Those who have several sexual partners and are not immunized are more likely to transmit sexual diseases**.(5)**

Genotypes

There are group-specific antigenic determinants in the hepatitis B surface antigen (HBsAg), which is produced from various HBV strains. HBV can be divided into four serotypes with distinct regional distributions, adw, adr, ayw, and ayr, based on varying serological reactivities of HBsAg. Furthermore, at least ten HBV genotypes (A to J) and many subtypes have been identified, each with a distinct geographic distribution, based on the homogeneity of the virus sequence and >8% or 4-8% genetic divergence**.(6)**

-HBV genotype A

HBV genotype A viruses are found in North America, South and East Africa, and Western Europe; nevertheless, these regions' HBV genotype A viruses are distinct sub-genotypes, and mounting data indicates that these regions' separate natural histories differ greatly. Young boys with the African HBV subgenotype (A1 or Aa) of HBV genotype A, for example, which frequently become HBeAG-negative and anti-HBe-positive, have low amounts of HBV DNA, and develop cirrhosis seldom, are associated to HCC**.(7)**

-HBV genotype B

HBV genotype B, one of Asia's two major HBV genotypes, is divided between two categories: Bj, found in Japan, and Ba, found elsewhere on the continent. HBV subgenotype Ba is associated with more serious liver disease, a higher risk of HCC, an older age at the time of HBeAg seroconversion, and a greater prevalence of mutations in the basal core promoter as compared to HBV subgenotype Bj**.(7)**

-HBV genotype C

Another noteworthy HBV genotype in Asia is HBV genotype C, which is possibly the most pernicious of the HBV genotypes. Numerous population-based and clinic-based prospective trials have produced persuasive evidence that HBV genotype C is independently linked to a greater risk of HCC compared to other HBV genotypes. For those with HBV genotype C infection, the average age of HBeAg seroconversion is 47 years old**.(7)**

-HBV genotype D

HBV gentotype D, which is present in northern Africa, Southern and Eastern Europe, and the eastern Mediterranean region, is associated with early HBeAg seroconversion. People with HBV genotype D infection in the latent phase of hepatitis B, on the other hand, are more likely to remain in this phase without developing liver disease or HCC**.**

Pathogenesis

Hepatocytes with full cellular differentiation are the main cell type infected with HBV. It seems that the cell-mediated immunological response to viral infection, which causes inflammation and necrosis, is the main factor responsible for the loss of hepatic cells. The cytotoxic T lymphocytes that are implicated respond only to the nucleocapsid protein fragments (HBcAg and HBeAg) that are expressed on the surface of infected hepatocytes. By getting rid of virus-producing cells, this reaction also helps to regulate the infection. Increased interferon-y production and natural killer cell activity can also restrict the spread of infection. The neutralizing antibody, anti-HBsAg, does not show up until much later in the convalescence phase, although it might help remove any free virus that is still in circulation at that point. More significantly, this antibody offers defense against reinfection**.(8)**

Clinical Manifestations and complications

When first infected, most people show no symptoms at all**.**

Some people suffer acute illnesses that persist for a few weeks at a time. Skin and eye yellowing (jaundice) dark urine, extreme fatigue, nausea, vomiting, and abdominal discomfort.Acute hepatitis can cause fatal liver failure if it is severe enough**.**

Serious side effects from a persistent HBV infection include:

Liver cirrhosis: Hepatitis B infection-related inflammation can cause cirrhosis, or significant liver scarring, which can compromise the liver's capacity to function**.**

Liver tumor: A prolonged infection with hepatitis B raises the chance of developing liver cancer, such as hepatocellular carcinoma**.**

Liver failure: Acute liver failure is a medical disorder where the liver stops functioning normally. When that happens, the only way to survive is to have a liver transplant**.**

Hepatitis B viral reactivation: Hepatitis B viral recurrence is typical in patients who have had their immune systems suppressed by chronic hepatitis B. Liver failure or severe damage may result from this. This includes patients receiving immunosuppressive drugs, such as chemotherapy or high-dose corticosteroids **.(9)**

Host Interactions

The capacity for viral clearance following a severe infection (or vice versa in the event of infection chronicization) and the onset of liver damage are both highly impacted by HBV and the host's immune system interactions. The effectiveness of the HBV-specific adaptive immune cell response has a significant impact on the course of most infections**.**

Depending on the host's age and immune system proficiency, the immune system will react differently to a virus. When immunocompetent subjects get HBV in adulthood, almost 95% of them go on to have a self-limited infection. The virus is successfully eradicated by the immune system following the acute phase. In contrast, most infections contracted during early childhood or infancy result in chronic illness. The adaptive immune response, which includes neutralizing antibodies and CD4+ and CD8+ T cell responses, is more engaged in these processes than the innate immune response. By killing infected hepatocytes and releasing antiviral cytokines (TNF, interferon-, and tumor necrosis factor, TNF), HBV-specific CD8+ T cells are the principal agents of viral clearance in infection cases that lead to recovery**.(3)**

Investigations
Blood is the preferred specimen for HBV infection diagnosis. Usually used for diagnostic screening, serological tests for viral antigens and antibodies can be run on either serum or plasma. HBV antigens and antibodies can be kept for days at room temperature and months at 4°C**.(9)**

-HBsAg
If the findings are negative, a long-term infection with HBV is typically ruled out**.**
If the test results are positive, the patient is suspected of having HBV. A persistent infection is established when HBsAg is found for longer than six months**.**

-Anti-HBs
Negative findings suggest that the patient is not resistant to HBV
If the result of the test is positive, the patient is assumed to be immune to HBV (either from a past infection or from another vaccine). Less than 1% of chronic carriers will ever test positive for both HBsAg and anti-HBs, a hepatitis B surface protein-binding antibody. In such cases, the patient is considered infectious**.**

-Anti-HBc
If negative, previous HBV infection is usually ruled out**.**
If the result is positive, the patient has an HBV infection. The infection could be continuing (HBsAg-positive) or resolved (HBsAg-negative). The individual is thought to be naturally immune to HBV infection if the infection is treated**.**

-HBc-igM
When HBsAg and anti-HBs tests are negative during the first stages of recuperation or "window period," anti-HBc-immunoglobulin (Ig) M may be the sole HBV marker detected. Anti-HBc-IgM tests, which are frequently positive with acute HBV infection, are no longer required to diagnose active infection because HBsAg assays are now highly sensitive**.(4)**

Prevention
A vaccination can prevent hepatitis B. The hepatitis B vaccination ought to be given to every newborn as soon as possible (within 24 hours). The hepatitis B vaccination is then administered in two or three doses, separated by at least four weeks. Once the three-dose immunization series has been completed, booster shots are typically not necessary. Hepatitis B is prevented by the vaccine for at least 20 years. Strict aseptic precautions should also be followed**.(5)**

Hepatitis C
Introduction
It has been almost 30 years since the discovery of hepatitis C virus by Michael Houghton, Harvey Alter, and Charles Rice for which they are awarded 2020 Nobel Prize in Medicine. Hepatitis C virus is a single-stranded RNA virus related to the flavivirus family. This virus has a high mutation rate, leading to the presence of six major genotypes and many subtypes. Those genotypes have different geographical distribution and different response to treatment **.(10)**

Mode of Transmission
Hepatitis C virus is a blood-borne pathogen. The vast majority of hepatitis C virus infections are transmitted through unsterilized medical equipment especially syringes and needles, IV drug abuse and needle sharing, unscreened blood transfusion. The risk of infection from a needle-stick injury is considerably low when compared to the risk of infection with hepatitis B virus. Vertical transmission remains a spot of controversy, some researches state that hepatitis c virus is transmitted through the placenta, while other researches state that it is transported via milk from a carrier or infected mother. The mode of transmission of hepatitis C virus remains a spot of controversy, as about 20-40% of HCV infections are of an unknown source**.(10)**

Pathogenesis
Viral particles circulating in the blood stream bind to lipoproteins and attach to various cellular receptors such as: CD81, SR-B1, LDL-R, EGFR, and EphA2. These receptors facilitate the attachment of the virus to the cellular membrane Through clathrin-mediated endocytosis, the virus penetrates the cell. After endocytosis, HCV particles develop in acidic endosomes, which stimulate HCV fusion that is pH-dependent at low levels,

and eventually release HCV genomic RNAs (un-coating) into the cytosol. As HCV is a positive-strand RNA virus, it enters the target cell through receptor-mediated endocytosis and release its genomic RNAs for translation in the cytosol **.(11)**
HCV can also spread to adjacent cells. A recent study stated that the HCV core genes were essential for the cell-to-cell transmission. However, the pathogenesis of how cell-to-cell transmission occurs is still lacking **.**
Replication of HCV virus in a host cell is still a weak spot and lacks a lot of studies. However, it has been suspected that this virus takes advantage of liver-specific micro-RNA called miR-22. This micro-RNA is suspected to increase the synthesis of HCV mRNA**.(11)**

Host Interactions
HCV RNA binds to pattern recognition receptors on hepatocytes through specific mediators and releases interferons. The release of interferons stimulates NK cells activation which release tumor necrosis factor. The tumor necrosis factor is an important cytokine that plays a major role in dendritic-cells maturation. Dendritic cells in turn, release interlukin-12 that binds to CD8 T-cells. CD8 T-cells initiate cytolysis of HCV infected hepatocytes**.(12)**

Clinical Manifestations and Complications
HCV infects hepatocytes primarily, but there is no evidence of it causing cytopathic effect. Rather, the affection of hepatocytes is immune-mediated and caused by immune attack by cytotoxic T-cells Persistent infection and chronic hepatitis are the hallmarks of HCV infection, despite the generally asymptomatic nature of the acute illness. Hepatitis C virus infection is mostly sub-clinical. Extra-hepatic manifestations are common but not specific. Symptoms such as arthralgia, myalgia, and pruritus are the most commonly occurring extrahepatic manifestations. In chronic stages, symptoms such as fever, easy fatiguability, melena, and jaundice are more common. A significant portion of infected patient might develop to liver cirrhosis, which is predisposing to hepatocellular carcinoma and liver failure **.(12)**

Investigations
Lab diagnosis of HCV could be further subdivided into serology, biochemistry, molecular assays, pathological assays, and radiological examination. Serologically, ELISA and RIBA could be used to detect Anti-HCV Ab and Core Ag. Serology is widely used to detect an HCV infection, however; it cannot differentiate between acute and chronic infection. This is where molecular assays show up. Today, commercial quantitative HCV-PCR methods have a very high specificity and sensitivity, the latter because nowadays considerably larger sample volumes are purified than was possible in the past. Absence of HCV-RNA in the blood after the end of treatment remains the best marker of sustained virological response (SVR) (13). HCV core antigen (HCV Ag) testing was introduced soon after the first HCV-PCR assays were available. Initially, the HCV Ag tests had a lower sensitivity than the HCV-PCR tests and therefore did not gain traction in Western countries. Since then, HCV Ag tests have become more sensitive and specific, and in countries where HCV-PCR tests are either very expensive or difficult to access, HCV Ag tests are a good alternative. Serology and molecular assays could interpret if a case is acute or chronic **.(14)**

Prevention
Unfortunately, HCV cannot be prevented by vaccination. Avoiding actions that can transmit the disease, such as injecting drugs using non-sterile injection equipment, is the best defense against hepatitis C. When someone comes into touch with blood from an infected person, they run the risk of contracting hepatitis C. As a huge number of HCV cases are asymptomatic, routine testing and screening is a recommended way of prevention **.(15)**

Hepatitis D
Introduction
In the last decade, Hepatitis D virus was thought to be an unrecognized HBV antigen. The HDV nuclear antigen is considered a hybrid virus since it uses the HBV surface antigen (HBVsAg) as its envelope protein. Thus, HDV infection is exclusive to patients with HBV **.(17)**

Mode of Transmission
HDV infections can be either acute or chronic and it is transmitted parenterally. HDV independently replicates inside the hepatocytes taking advantage of HBVsAg as its envelope protein. Direct cytotoxic effects of HDV

or host-mediated immune responses leads to hepatocellular necrosis. It is uncommon for HDV to be transmitted perinatal and the risk factors include I.V drug abuse, blood transfusions and sexual contact**.(18)**

Pathogenesis

HDV is made up of a lipoprotein envelope consisting from: HBVsAg, RNA genome, and hepatitis D antigen (HDVAg). The HDVAg are named after their size and there are two types, long and short. The long antigen directs viral assemble with inhibiting viral replication. On the other hand, the short HDVAg activates viral replication by binding directly to the HDV RNA and then become completely assembled by the incorporation of HBV envelope. Hepatitis D virus is unique due to its ability to use the host RNA polymerase II to transcribe its own messenger RNA **.**

Individuals who are infected by HBV only can be infected by HDV. If there is no presence of HBV then they are not susceptible to HDV. Being infected with both viruses simultaneously can result in an acute hepatitis B and D infections which is clinically same as HBV with the exception of biphasic course of two peaks of serum alanine aminotransferase (ALT). This is due to HBV being established first during the acute co-infection before HDV starts spreading. The majority of patients recover during the acute phase with only about 5% developing to chronic phase which is defined by the persistence of the infection for more than 6 months. Chronic hepatitis D can be more severe than B and causes more complications such as cirrhosis, hepatocellular carcinoma, progressive fibrosis, and hepatic decompensation**.(19)**

Clinical Manifestations

HDV doesn't really differ much from other types in the clinical symptoms and the majority of the patients are asymptomatic. Signs usually includes jaundice, abdominal pain, bruising, fever, and depending on the severity it can cause bleeding**.(19)**

Host Interactions

Although the exact method by which HDV causes liver damage is unknown, the host immune response is considered to be responsible. Damage might range from complete liver failure to no symptoms at all. HDV superinfection raises the risk of hepatocellular cancer and typically progresses more quickly. The host immune response, the HBV genotype, and the HDV genotype are among of the variables that affect the extent of harm. There are three primary HDV genotypes known to exist: genotypes 1, 2, and 3. Other genotypes have also been found, albeit they are not as well defined as these. In Western countries, genotype 1 is the most common type. In cases where acute hepatitis D is present, the condition progresses rapidly. Once chronic, it can make HBV condition that already existed worse. It can either go slowly or quickly in the direction of liver cirrhosis. Genotype 2 is predominantly found in the Far East's nations. It is not as frequently associated as genotype 1 with the development of fulminant liver disease and chronic liver disease. In South America, genotype 3 is the most prevalent genotype. It frequently causes severe acute hepatitis, which can result in liver failure**.(20)**

Investigations

Serological indicators such as HDAg and anti-HDV antibody (anti-HDV) are used to determine if an individual has HDV infection. IgM anti-HDV is detectable at high titers, which indicates chronic infection. It is detectable throughout the 'window' phase of the infection, prior to the production of IgG anti-HDV. Every HDV-infected person develops anti-HDV antibodies, either of the IgM or IgG class. This is a universal sign of the infected host's innate and adaptive response. Since anti-HDV IgG antibodies can linger for years even after HDV infection has cleared up, all HBsAg-positive patients should have this test, which is typically performed as part of epidemiological surveys for HDV infection. In contrast, IgM anti-HDV decreases but eventually remains in patients with self-limited infections and progress to chronicity. Since HBV is the host for HDV, determining HBV replication and indicators is essential to the diagnosis of liver disease. In chronic HDV carriers, HBsAg levels appear to be correlated with HDV viremia **.(21)**

Usually, internal qualitative or semi-quantitative RT-PCR techniques are used to detect serum HDV RNA. Although a number of semi-quantitative techniques have been put forth, they are still challenging to implement and compare. Both the amplified area and the various HDV genotypes can affect the sensitivity of HDV RNA detection**.(22)**

Prevention

There is no vaccine to prevent hepatitis D. However, it cannot occur in the absence or hepatitis B so vaccination against hepatitis B is the only method of preventing hepatitis D**.(23)**

Hepatitis E

Introduction

HEV is a non-enveloped, single-stranded RNA virus belonging to the Hepeviridae. The Hepeviridae family encompasses two genera: piscihepevirus and orthohepevirus. Hepatitis E virus (HEV) is the primary causative agent of acute viral hepatitis on a global scale. HEV transmission takes place predominantly through the gastrointestinal tract and is responsible for outbreaks in industrialized countries as well as animal cases in developing as well as advanced nations. HEV genotypes HEV1 and HEV2 are solely present in humans and predominate in underdeveloped nations. Additional gene variants, such as HEV3 and HEV4, have been found in humans as well as livestock, with pigs representing the principal carriers **.(24)**

Mode of Transmission

Hepatitis E virus (HEV) exhibits genetic diversity, and four main genotypes, namely genotypes 1-4, have been identified. Genotypes 1 and 2 are predominantly found in developing countries and are commonly transmitted through the fecal-oral route, specifically via contaminated water sources. In these regions, inadequate sanitation and water treatment contribute to the high prevalence of HEV genotypes 1 and 2**.(24)**

On the other hand, genotypes 3 and 4 are capable of infecting both individuals with intact immune systems (immune-competent) and those with compromised immune systems (immune-compromised). Strains of HEV belonging to genotypes 3 and 4 are associated with zoonotic infections transmitted through the consumption of contaminated food. Specifically, the consumption of uncooked or undercooked meat and products derived from swine, wild boar, or deer can serve as a source of transmission for HEV genotypes 3 and 4**.**

In addition, HEV can also be transmitted through other routes. Blood transfusions and organ transplants have been identified as potential routes for HEV transmission. Approximately 70% of solid organ transplant patients infected with HEV develop chronic hepatitis. It is important to note that the transmission routes and prevalence of HEV genotypes may vary across different geographical regions and populations. Understanding the specific transmission patterns and risk factors associated with each genotype is crucial for implementing appropriate preventive measures and public health interventions**.(25)**

Pathogenesis

HEV1 and HEV3 replication have been demonstrated in intestinal cells, and the presence of HEV RNA and ORF2 antigen has been found in the crypts of a chronically infected patient. These findings suggest that HEV initially undergoes multiplication in the intestine before entering the liver through the bloodstream. Subsequently, it may then proliferate in the cytoplasm of hepatocytes and be discharged as lipid-associated particles. Previous in vitro studies using polarized hepatocytes have demonstrated that the bulk of HEV fragments discharge at the apical membrane, which corresponds to the bile portion. The lipids associated with the virus released in feces are then removed by bile salts. As HEV does not exhibit direct cytopathic effects, liver damage resulting from HEV infection is believed to be immune-mediated, involving cytotoxic T cells and natural killer cells**.(26)**

Clinical Manifestations and complication

Hepatitis E virus (HEV) infection can present with a range of clinical manifestations, including both asymptomatic cases and symptomatic cases. In symptomatic cases, the onset of symptoms typically occurs within 2–6 weeks after exposure to the virus**.**

The most common symptoms of hepatitis E include fever, fatigue, nausea, vomiting, abdominal pain, and jaundice. Elevated liver enzymes, such as alanine aminotransferase (ALT), are often observed, indicating liver inflammation and injury. Additionally, hepatitis E infection has been associated with extra-hepatic manifestations, including acute pancreatitis, because the virus can invade the pancreas, leading to direct inflammation and destruction of pancreatic acinar cells. Furthermore, hepatitis E infection has been linked to various neurological manifestations. These include Guillain-Barré syndrome, Bell's palsy, and neuralgic amyotrophy. It is believed that HEV has the ability to cross the blood-brain barrier and invade the brain and spinal cord, resulting in neurological complications**.(27)**

Host Interactions

Hepatitis E virus (HEV) exhibits a complex interplay with the host's innate immune responses, both activating and evading them through various mechanisms. Upon HEV infection, the viral genome is recognized by pattern recognition receptors (PRRs), including retinoic-inducible gene-I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and Toll-like receptor 3 (TLR3). This recognition triggers signaling cascades leading to the activation of the type I interferon (IFN) response**.**

Following HEV infection, IFN regulatory factor 1 (IRF1) inhibits viral replication by activating the signal transducer and activator of transcription 1 (STAT1) and inducing the expression of IFN-stimulated genes (ISGs). In addition, HEV's ORF3 protein interacts with the N-terminal domain of RIG-I, promoting RIG-I production and activation and potentially enhancing antiviral signaling. HEV has evolved molecular evasion mechanisms to avoid detection by the host immune system, employing direct and indirect strategies. Firstly, the HEV papain-like cysteine protease (PCP) inhibits IFN induction triggered by RIG-I and TANK-binding kinase 1 (TBK1) by downregulating K63-linked ubiquitination, thus suppressing the activation of downstream signaling. Secondly, the HEV X protein hinders the TBK1-mediated phosphorylation of IRF3, impairing its activation and subsequent IFN production**.(28)**
Furthermore, the HEV ORF3 protein actively modulates the innate immune response through several mechanisms. It activates signal regulator protein alpha (SIRP), which initiates a negative feedback loop to dampen the immune response. ORF3 also inhibits the phosphorylation of STAT1, preventing its activation and attenuating the expression of ISGs in response to IFN**.**
These intricate interactions between HEV and the host's innate immune system highlight the virus's ability to both trigger antiviral responses and employ evasion mechanisms. Understanding these mechanisms is essential for developing effective antiviral strategies and vaccines against HEV**.(28)**

Investigations
Detection of virus
HEV RNA is detected through the use of nucleic acid testing (NAT) methods such as polymerase chain reaction (PCR). During the incubation period and early symptomatic phase of acute HEV infection, individuals typically exhibit the highest levels of viremia. The excretion of HEV in feces is temporary. In immunocompromised patients, where HEV RNA persists for three months or longer, spontaneous viral clearance is unlikely to occur**.(27)**

Diagnostic Testing
Anti-HEV IgM levels typically reach their highest point prior to the onset of clinical symptoms, so they can serve as an early diagnostic marker for detecting HEV infection. but remain elevated for approximately 8 weeks before rapidly declining. In individuals with acute hepatitis, the presence of anti-HEV IgG antibodies is commonly observed. The levels of anti-HEV IgG antibodies peak approximately 4 weeks after the initiation of symptoms and remain elevated for more than a year **.(28)**

Prevention
Population-level Prevention:
Ensuring high-quality public water sources: viruses from water sources**.**
Establishing suitable human feces disposal systems

Individual Prevention:
Practicing good hygiene:
Avoiding the use of contaminated water: Drinking safe and properly treated water, such as boiled or bottled water, is recommended**.**
Safe food practices: HEV can be transmitted through the consumption of undercooked or raw meat, particularly pork and wild game. Cooking meat thoroughly, ensuring it reaches a safe internal temperature, can help inactivate the virus and reduce the risk of HEV infection**.**

Vaccine (Hecolin®)
Hecolin® is a virus-like particle (VLP) vaccine developed through genetic engineering techniques. The vaccine employs the ORF2-encoding gene derived from a strain of HEV genotype I. Innovax Biotech has established a production procedure utilizing a 50-liter fermentation tank for the cultivation of the vaccine. Recombinant proteins are refolded to generate VLP particles. The final product is provided in pre-filled syringes, with the antigen adsorbed to aluminum hydroxide and suspended in buffered saline**.**
The vaccination regimen for Hecolin® consists of a series of three doses, each containing 30g of the vaccine in a 0.5-ml volume. These doses are administered at 0, 1, and 6-month intervals. This manufacturing technology is straightforward to scale up, facilitating efficient quality control measures. Although the current production capacity of Hecolin® at Innovax Biotech stands at approximately 200,000 doses per year, the company has substantial potential to increase output to 500,000 doses per year, as per their manufacturing

capacity planning. Consequently, Hecolin® is poised to meet the global demand for HE vaccinations in the future**.(29)**

Treatment

Hepatitis A:

Hepatitis A has no particular treatment. The majority of hepatitis Patients usually recover in six months. The goal of hepatitis A treatment is typically to maintain comfort and manage symptoms. Rest may be necessary. Many hepatitis A patients experience fatigue, nausea, and decreased vitality. While consuming enough food and liquids is beneficial, adequate food intake might be challenging when experiencing nausea **.(2)**

Hepatitis B :

Treatment options for long-term hepatitis B could be antiviral drugs such as entecavir, tenofovir, lamivudine and adefovir, These medications are ingested orally. To enhance treatment response, these drugs should be administered alone or in combination with interferon. There is also Interferon shots. Interferon alfa-2b (Intron A) is an artificial version of an infection-fighting molecule generated by the body. It is mostly used for young persons with hepatitis B who want to avoid long-term treatment, as well as women who desire to become pregnant within a few years of finishing a limited course of medication. During interferon therapy, women should utilize contraception. Interferon should not be given to a pregnant woman. Nausea, vomiting, trouble breathing, and depression are all potential side effects. A liver transplant can be an option with sustained significant damage **.(9)**

Hepatitis C:

Tablets called direct-acting antivirals (DAAs) are used to treat hepatitis C. The safest and best medications for treating hepatitis C are DAA pills. Over 90% of patients find them to be quite efficient in curing the condition. The 8-to-12-week course of pills is taken. Depending on the type of hepatitis C, the course of therapy will vary. More than one kind of DAA can be used to treat some forms of hepatitis C **.(14)**

Hepatitis D:

The goal of the current course of treatment is to avoid complications related to HDV. Even in cases when undetectable levels cannot be reached, treatment aimed at lowering HDV RNA levels has been demonstrated to have better results.5. The goals of treatment should be to normalize liver enzymes and inhibit HDV replication, which is thought to be reduced by at least ≥2 log at the conclusion of the regimen. For the primary therapy of HIV, pegylated interferon-alpha (Peg-IFN-alpha) is the preferred medication. Because of its advantageous antiviral and immunomodulatory properties, type I interferon IFN-alpha is frequently used to treat a variety of viral infections. Peg-IFN-alpha has demonstrated helpful virological response rates during therapy; nevertheless, modest rates of HDV RNA negative have been observed 24 weeks following termination. Furthermore, over 50% of responder patients experience late relapses, and there is little information to determine the ideal course of treatment. In light of the lack of data about the optimal duration of treatment, it is recommended that Peg-IFN-alpha be continued for 48 weeks regardless of response, provided that it is well tolerated. The serious side effects of Peg-IFN-alpha, which include cytopenias, depression, and flu-like symptoms, are one of its drawbacks. Furthermore, in cases of decompensated liver disease, Peg-IFN-alpha should be avoided; liver transplantation is one of the few choices that remains**.(22)**

Hepatitis E:

HEV 239, a subunit antigen including amino acids 368-606 manufactured by E. coli, and 56-the Kansas Development Authority subunit antigen containing amino acids 112-607 of ORF2 expressed by cultured insect cells, have both been developed as vaccines against HEVs. Only HEV 239 is available in China, and it is the only one having a human use authorization. The Hecolin® vaccine provides cross-protection for genotypes 1 and 4 and was designed to generate protective antibodies against all HEV genotypes. The efficiency of this three-dose vaccine is 97% based on measurements of long-term efficacy during follow-up and the capacity to prevent episodes of symptomatic acute hepatitis. According to simulation tests, it can provide protection for up to thirty years. Women who are pregnant are safe taking this medication**.**

Non-Viral Hepatitis:

One possible course of treatment for toxic hepatitis is to cease exposure to the chemical that caused it, limiting alcohol intake and minimizing excessive use of over-the-counter medications, herbal remedies and supplements. Corticosteroids are also prescribed to treat hepatitis symptoms**.(28)**

Conclusion

Hepatitis A is a liver-related inflammation caused by the Hepatitis A virus (HAV). There used to be two infection patterns, but in 1973 the symptomatic pattern was given the designation "Hepatitis A." Travel to endemic regions, food, water, and sanitation are the main routes of transmission. Next, hepatitis B is an acute or chronic liver infection caused by the hepatitis B virus. Blood, saliva, vaginal fluids, infected blood, and semen can all spread it. The majority of viral transmission occurs either vertically or horizontally, especially between children who are sick and those who are not. After viral infection, hepatocytes that have reached complete cellular differentiation become inflamed and necrotic due to the cell-mediated immune response. Then, the single-stranded RNA virus known as the Hepatitis C virus, which was identified by Houghton, Alter, and Rice in 2020, has six main genotypes and subtypes. The main routes of transmission are via shared needles, unscreened blood transfusions, IV drug misuse, and contaminated medical equipment. Viral particles bind to cellular receptors and lipoproteins during pathogenesis. Subsequently, only HBV patients can get the hybrid virus known as hepatitis D, which can spread acutely or chronically. Hepatocellular necrosis results from its replication, which is facilitated by the envelope protein HBVsAg. Because it can use host RNA polymerase II, HDV is unique. severe complications can arise from both acute and chronic infections. Following the Hepatitis E virus (HEV) is a non-enveloped, single-stranded RNA virus from the Hepeviridae family. It is the main worldwide source of acute viral hepatitis, mostly spread by the gastrointestinal tract. While HEV genotypes 3 and 4 can infect both immune-competent and immune-compromised people, genotypes 1 and 2 are mostly common in underdeveloped nations. Understanding genotypes is essential for public health treatments and preventative actions since different regions have different transmission patterns. Next comes the non-viral types of hepatitis, called autoimmune hepatitis, which is caused by the body's immune system attacking the liver and causing significant inflammation and death of liver cells. Type 1 and Type 2 are the two main categories that might result in coexisting autoimmune diseases. Finally, the treatment, there is no particular therapy for hepatitis A, and the majority of patients do not suffer significant long-term effects. The goals of treatment are to control symptoms and preserve comfort. Antiviral medications that inhibit the virus's ability to damage the liver include entecavir, tenofovir, lamivudine, adefovir, and telbivudine. Young adults with hepatitis B who want to avoid long-term therapy or women who may wish to get pregnant can use the interferon injections. Individuals with severe damage may be suitable for liver transplants. Over 90% of patients find direct-acting antivirals (DAAs) to be helpful in treating hepatitis C. The goals of treatment are to stop HDV replication and return liver enzymes to normal. For primary HIV treatment, pegylated interferon-alpha (Peg-IFN-alpha) is the recommended drug. Hepatitis E vaccines like HEV 239 and 56-kDa subunit antigens offer cross-protection for both genotypes. Non-viral hepatitis treatments include avoiding exposure to the causing chemical, taking prescription drugs, and getting a liver transplant**.**

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