Hepatitis A: An Overview

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ABSTRACT

Hepatitis A, caused by the hepatitis A virus (HAV), remains a consequential global public health concern. This chapter provides a comprehensive overview of the virology, pathogenicity, zoonotic transmission, epidemiology, clinical manifestations, and prevention strategies associated with hepatitis A. Hepatitis A is caused by non-enveloped virus belongs to the family Picornaviridae. It has a limited scope for zoonotic transmission, but it is widely distributed in human population with varying prevalence rates across different regions. Factors such as contaminated food and water sources, and crowded living conditions with poor sanitation contribute to the transmission of the virus. The disease predominantly affects low and middle-income countries, emphasizing the understanding of its socio-economic implications. Clinical features of hepatitis A range from asymptomatic infections to severe liver disease. The virus primarily targets the liver, leading to symptoms such as jaundice, fatigue, nausea, and abdominal pain. Vulnerable populations, including young children and older adults, are at a higher risk of getting severe complications. Timely diagnosis through serological testing is crucial for proper public health management and interventions. Prevention strategies play a pivotal role in controlling the spread of hepatitis A. Vaccination campaigns targeting high-risk populations have proven to be effective in reducing the incidence of infection rate. In conclusion, hepatitis A remains a significant challenge with diverse clinical presentations and global distribution. By fostering a deeper comprehension of the virus and its modes of transmission, healthcare professionals, policymakers, and researchers can contribute to the development of effective strategies to mitigate the impact of Hepatitis A on public health. Ongoing efforts to enhance vaccination coverage, improve sanitation infrastructure on individual and public level, and raise awareness about hygienic practices are crucial for reducing the burden of hepatitis A and preventing its associated complications.

Keywords: Hepatitis A, Infectious Hepatitis, Enterovirus, Jaundice, Fulminant Liver.

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1. INTRODUCTION

Hepatitis is a contagious systemic illness that infects the liver. Initially, only two patterns of hepatitis were noted, named "infectious hepatitis" for clinically apparent infection and "serum hepatitis" for clinically inapparent infection, respectively. These two early forms of hepatitis got differentiation when the Australian antigen was discovered on the surface of the hepatitis B virus. Serum hepatitis was called hepatitis B, and infectious hepatitis was called Hepatitis A (Blumberg et al. 1967). Now, hepatitis has many types; Hepatitis A, B, C, D and E. Hepatitis B and C are the leading cause of chronic illness, while other viruses cause acute illness (Gholizadeh et al. 2023). The hepatitis A virus was characterized in 1973 from human fecal material using an electron microscope by Feinstone and his colleagues (Feinstone et al. 1973; Koff et al. 2002). Complete hepatitis A viral culture was studied a few years later than its discovery (Fig. 1) (Martin and Lemon 2006).

The causative agent of hepatitis A is a non-enveloped hepatitis A virus (HAV). It is an enterovirus (positive single-stranded RNA virus) that belongs to the family Picornaviridae (Fox et al. 2015).

Primarily, hepatitis A (formerly called "infectious hepatitis") is an acute viral disease that affects humans, but in rare cases, it has also been associated with zoonotic transmission. Hepatitis A virus (HAV) is highly contagious that can cause mild to severe illness, ranging from imperceptible anicteric infection to fulminant liver (acute liver failure), and can cause death. Its transmission mode is the feco-oral route via contact with contaminated water, food, and an infected person (Acheson and Fiore 2004). HAV enters the body through ingestion and replicates itself in the patient's liver. Its incubation period is usually from 15-50 days, during which it replicates and remains present in blood and excretes via the biliary system into feces (Foster et al. 2021).

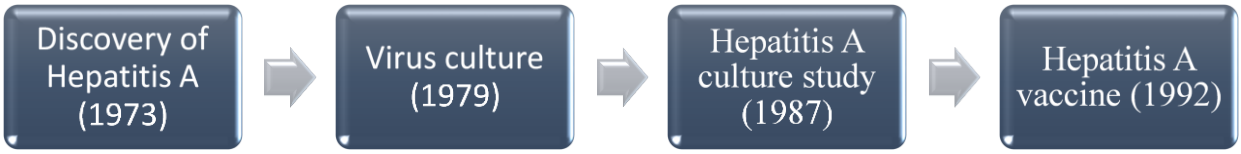

Fig. 1: Series of events after the discovery of the hepatitis virus

HAV can persist in the environment and spread epidemically and sporadically worldwide. Improper personal hygiene, inadequate sanitation, international traveling, oral-anal sex, and lack of safe food and water are the primary cause of getting the infection (WHO 2023). Every year HAV results in millions of cases globally. Based on HAV seroprevalence types, the globe can be divided into high, intermediate, low, and very low endemicity rates (Jacobsen 2018). Its outbreak and illness have lessened due to immunization and adopting health measures, but underdeveloped countries are still struggling with this virus. In highly endemic countries, inhabitants acquire hepatitis in their early childhood and become immune to it for the rest of their lives (Jacobsen 2009).

On the contrary, in less-endemic countries, inhabitants get this infection due to exposure to that environment or engaging in risky health behaviors (Aggarwal and Goel 2015). HAV has an asymptomatic appearance in small children. In developing countries, adults usually do not show clinical symptoms due to partial immunity, but in developed countries, adults show early symptoms. Humans are naturally

more susceptible to HAV and are the reservoir for infection than non-human primates. HAV circulation is limited to primates and is very rare in other vertebrates (Lanford et al. 2019). HAV has been reported in captive non-human primates like monkeys, chimpanzees, etc., where humans have close contact with these animals (Balayan 1992; Chichester et al. 2018). In this chapter, we will discuss virology, epidemiology, zoonotic transmission, clinical complications, and treatment of hepatitis A based on the latest available data.

2. VIROLOGY

Hepatitis A virus is a naked (non-enveloped) RNA virus, 27 nm in diameter, belonging to the genus Hepatovirus and family, Picornaviridae (Fig. 2). The Hepatovirus genus is specifically known to infect small mammals (Drexler et al. 2015). HAV is a very tough virion that can survive in the environment for at least one month and temperatures up to 85℃. Chlorine inactivation and heat-resistant properties make it intact against physical treatment (Lemon 1992; Cromeans et al. 2001).

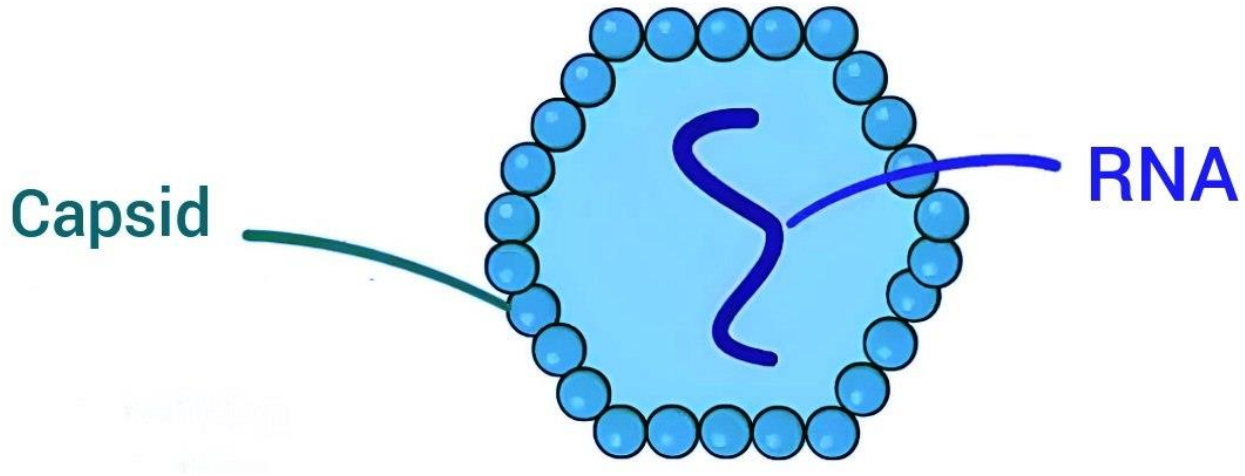

Fig. 2: Structure of Hepatitis A virus; non-enveloped, single-strand RNA genome (Retrieved from Paint)

2.1. SEROTYPE

Hepatitis A virus has only one serotype across the globe. Although it has nucleotide heterogeneity in its genome, this high preservation of nucleotides to hold a single serotype is due to the antigenic structure of the capsid. A person is fully protected from reinfection by other serotypes of HAV, even from different parts of the world. Anti-HAV preparations of immune globulin can give protection against disease irrespective of the geographic region because of the one serotype of HAV (Desbois et al. 2010).

2.2. GENETIC ORGANIZATION

HAV is a positive-polarity (i.e., translatable), single-stranded virus having 7470-7478 nucleotides in its RNA genome (Lin et al. 2017). It has two noncoding regions, a 5' region with ~734 nucleotides and a 3' region with 40-80 nucleotides, respectively. 5' end of the genome has no cap and is attached to a genome-linked viral protein (VPg), a protein primer for the synthesis of RNA (Weitz et al. 1986; McKnight and Lemon 2018). On the contrary, the 3' end terminates with a tail of poly A chain (Baroudy et al. 1985; McKnight

and Lemon 2018). A coding region of ~2225 nucleotides is present in the center of both terminals, which codes for viral proteins (Hollinger et al. 1996; Gholizadeh et al. 2023).

2.3. PROTEIN ARRANGEMENTS

The hepatitis A virus has 3 protein units (P1, P2, P3) as shown in Fig. 3. The structural proteins of the virus derive from the P1 region, and nonstructural proteins involved in the reproduction of the virus translate

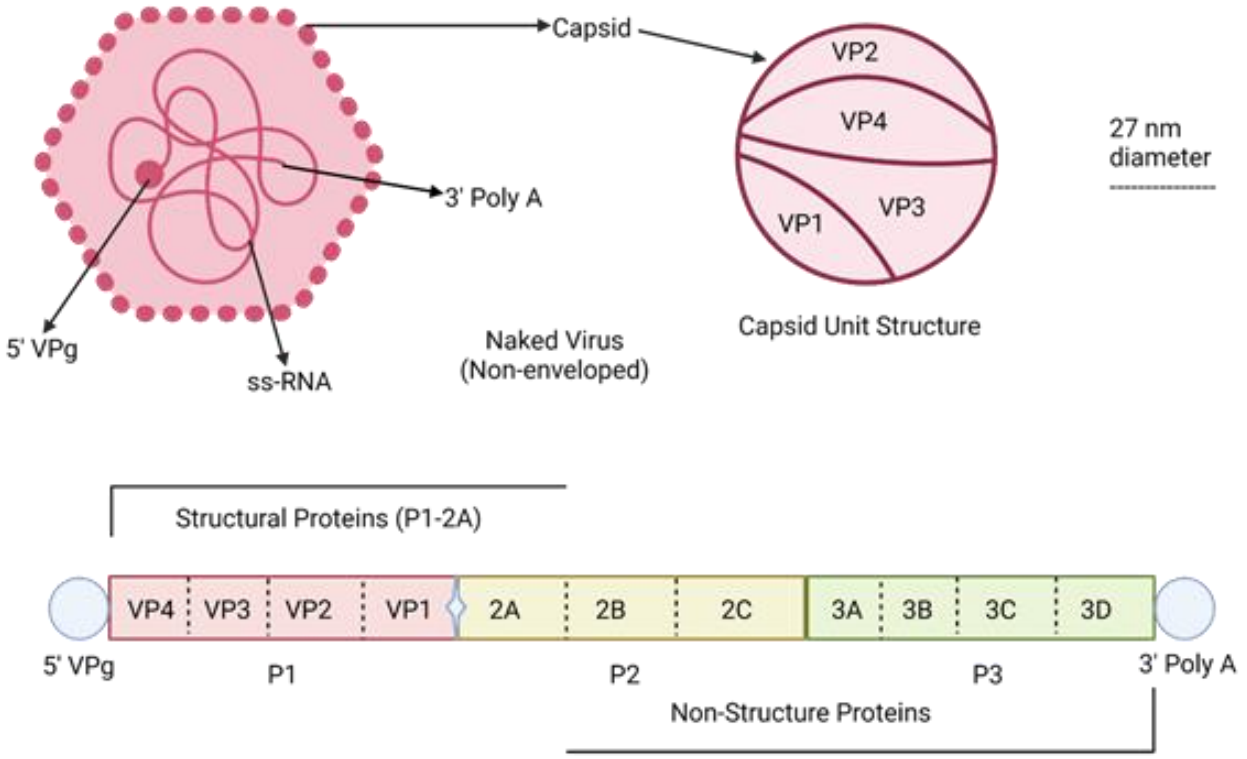

Fig. 3: Hepatitis A virus with its RNA structure having protein units (Retrieved from BioRender)

from P2 and P3 regions. P1 region forms the main proteins of the capsid, i.e., VP1-pX (VP1-2A), VP2, and VP3, along with VP4, which is necessary for virion maturation. These proteins are involved in capsid formation. VP4 protein is not detected in viral culture but only in mature viral particles (Cuthbert 2001). P2 and P3 regions have seven proteins, of which six mature proteins (2B, 2C, 3A, 3B, 3C, 3D) involved in RNA synthesis have nonstructural characteristics (Nainan et al. 2006). Several studies revealed a unique contribution of 2A protein in HAV morphology, but most of its characteristics are still unknown (Morace et al. 2008; Lemon et al. 2018).

2.4. GENOMIC DIVERSITY

HAV shows several genotypes and subgenotypes, although it has a very high degree of nucleotides and amino acids conservation (Robertson et al. 1992). According to the early classification, which facilitates the understanding of the zoonotic aspect, HAV has seven genotypes; four of which (I, II, III, VII) share a

human origin, and three of which (IV, V, VI) have the simian origin (Ching et al. 2002). In 1991, some scientists extracted and reported the simian origin serotypes as mentioned in Table 1.
All three simian genotypes have unique sequences of nucleotides on the P1 region, derived from the species of Old-World monkeys. Early studies showed that these three genotypes have unique signature sequences of nucleotides on capsid protein at VP1/VP3 junction, differentiating them from the human HAV strains (Brown et al. 1989). It has also been studied that non-human primates, i.e., bats, rodents, and shrews, have HAV strains that appear to share antigenicity with the hepatitis A virus of human illness (Williford and Lemon 2016).

Table 1: Non-human primates' strains of HAV, isolated from non-human primates

HAV genotype	Animal	Scientific Name	Imported	Reference
IV	cynomolgus macaque	*Macaca fasicularis*	Philippines	(Nainan et al. 1991)
V	African green monkey	*Cercopithecus aethiops*	Kenya	(Tsarev et al. 1991)
VI	cynomolgus macaque	*Macaca fasicularis*	Indonesia	(Nainan et al. 1991)

3. PATHOGENICITY

The pathogenicity of HAV generally depends upon the severity of the infection and the physiology of infected persons (Rezende et al. 2003; Belkaya et al. 2019). Some pathological events of HAV are described below.

3.1. VIRAL REPLICATION

The entrance route of the HAV in the body is the oral pathway. It replicates only in the targeted host cells. Primarily, it attacks the hepatocytes and binds with its cellular receptors. A recent study revealed that gangliosides are the promoting molecules of HAV entrance into the host cell (Nain et al. 2022). HAV enters the cell by receptor-mediated endocytosis. The viral capsid gets dissimilated, and its genome releases out of the capsid. The viral RNA serves as the messenger RNA for the host cell ribosomes and forms a polypeptide unit by translation. It is cleaved by viral protease (3C unit of the 3P region in the viral genome) to manufacture additional viral protein components (Feng and Lemon 2014; Yang and Zhang 2015). Henceforth, this cellular activity initiates the 3D unit in the P3 region of the viral genome to work as RNA-dependent polymerase (Enzyme) and replicates the RNA to make several copies as shown in Fig. 4. Newly synthesized viral proteins and a viral genome assemble to form a new virus, which releases the infected cell by exocytosis (Lemon 2010).

3.2. HEPATIC CYTOPATHY

Acute hepatitis A cause severe cytopathic effects. The liver, infected with the hepatitis A virus, gets inflammation and destruction of hepatocytes. The hepatitis A virus does not cause hepatic cell death, but the immune-mediated mechanism induces cytopathy of hepatocytes. After replication, a single HAV clones into multiple infectious virions. Activated immune cells, i.e., natural killer cells and macrophages, infiltrate the liver to combat the infection (Chen et al. 2018). T lymphocytes, cytokines, and chemokines play an essential role during hepatitis. T cells coincide with HAV-infected hepatic cells during this viremic phase. Virus-specific $CD8^+$ T cells contribute to the virus control and cause HAV-infected cell injury, thus increasing the ALT level in the blood. T cells also combat hepatitis A virus and control its proliferation in the blood. T cells, cytokines, and chemokines also increase the interferon level in the blood. These cells cause the hepatocytes to release INF-γ, which triggers the natural killer cells, and T cells to release

granzyme molecules. Granzymes are protease enzymes that induce programmed cell death in virus-affected hepatocytes. These hepatic cell deaths due to the hepatitis A virus ultimately result in liver inflammation (Maier 1988; Fleischer et al. 1990; Shojaie et al. 2020).

3.3. DUAL PHENOTYPES

HAV is recently discovered in two phenotypical forms, naked virion and quasi-enveloped virion (eHAV) (Feng et al. 2013). The quasi-enveloped virion is actually a naked virion, membraned by an exosome-like vesicle (McKnight et al. 2017). HAV exists in the bloodstream as a quasi-enveloped virus. eHAV is immature in the lipid-membraned exosome, containing VP1-pX protein. This form of HAV is responsible for the cell-to-cell transmission of virion. In the liver, the detergent-like action of bile salts in the biliary canaliculi releases the naked virion out of the exosome. The naked virion passes from the bile duct to small intestine and is shed into the feces (Hirai-Yuki et al. 2016). This form is the ultimate source of human-to-human viral transmission through feces (Fig. 5). The naked form of HAV is mature and has completely processed VP1 and 2A proteins in its genome (Feng et al. 2014).

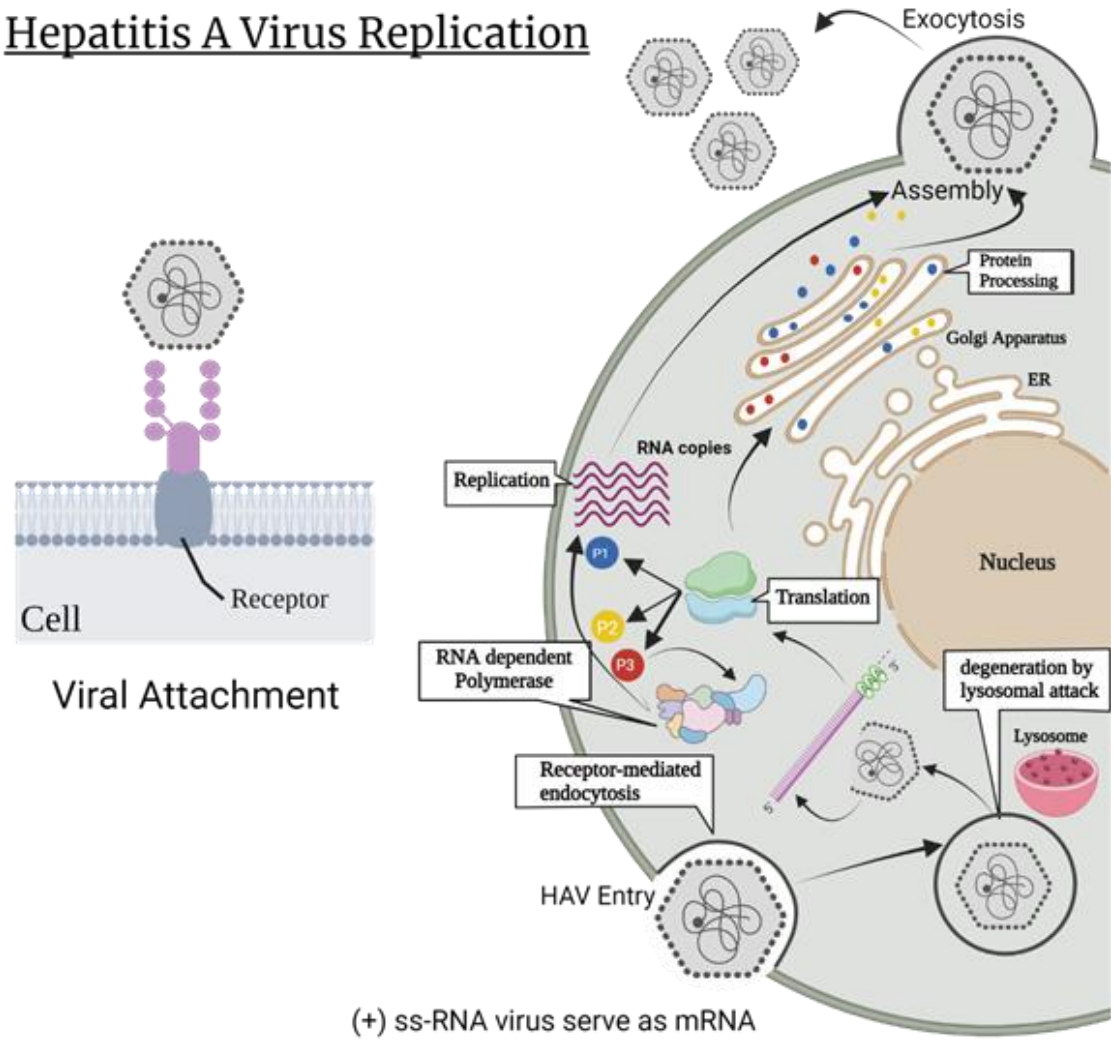

Fig. 4: Generalized replication process of HAV in the host cell of infected patient (Retrieved from BioRender).

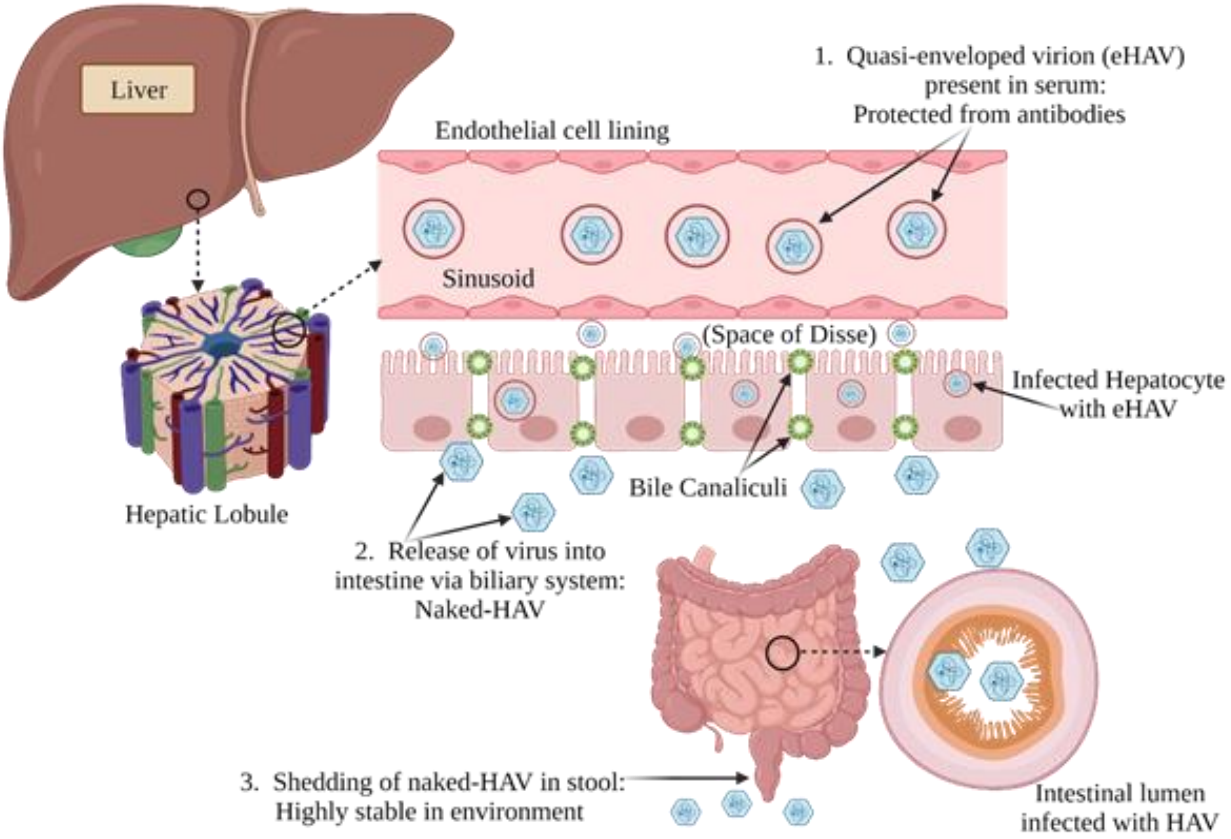

Fig. 5: Two morphological forms of infectious hepatitis A virus (HAV); Quasi-enveloped HAV exists in blood plasma, and naked HAV exists in feces (Retrieved from BioRender).

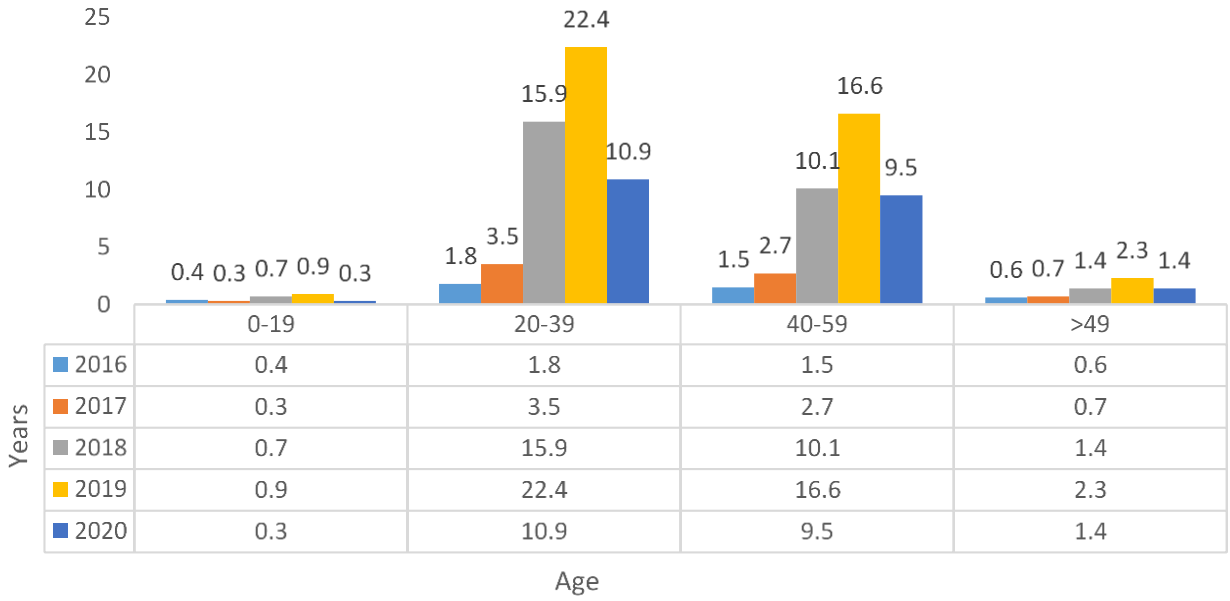

Fig. 6: Rate of HAV distribution per 1 lac population on the basis of CDC report.

4. TRANSMISSION

Hepatitis A virus is exceedingly transmitted through the feco-oral route. The virus is passed either through the ingestion of contaminated food or water materials or through direct contact from one infected person to another. Other potential transmission sources include travel to HAV-endemic countries, sexual contact, men having sex with men (MSM), occupational or nosocomial exposure, and infrequent parenteral transmission. Transmission of the Hepatitis A virus through blood transfusion is exceedingly rare due to the short persistence of viremia (Jeong and Lee 2010).

4.1. CONTAMINATED FOOD AND WATER

Drinking contaminated water, whether caused by poor irrigation infrastructure or inappropriate chlorination, is the potential source of HAV transmission in developing countries. Hepatitis A virus mostly persists in water bodies. It infects vegetative eating and defiles the drinkable water reserves of animals and humans (Ahmad et al. 2018). Many fruits, vegetables, fish, and other edible food become infected if they come into contact with this contaminated water during irrigation or cultivation. HAV transmission through eating improper food and water also includes public food-service workers. They neither sanitize their hands nor wash off serving glasses or plates properly (Schwarz et al. 2008). Sharing this contaminated silverware on public food courts or homes transmits the hepatitis A virus to a large community (Ahmad et al. 2018).

4.2. PERSON-TO-PERSON TRANSMISSION

An infected patient having direct contact with a healthy person causes the transmission of the hepatitis virus. Children are most likely to transmit the infection to their parents due to less scrupulous hygiene (Klevens et al. 2010). Some crowded living communities with less sanitation are also involved in the transmission due to their low standard of living. Moreover, sexual contact, particularly MSM and anal sex, is also a dramatic cause of HAV transmission in Europe and America (Bruisten et al. 2001; Nainan et al. 2005; Tanaka et al. 2019).

4.3. INTERNATIONAL TRAVEL

A healthy person traveling to regions of high HAV endemicity may acquire hepatitis infection because of the unsanitary environment and unhygienic local food of that region. On the contrary, one HAV-infected person can be the vector of this disease to an area with a low HAV rate. It is advisable to get one dose of HAV vaccination before your trip to that infected region (Steffen et al. 2004).

5. EPIDEMIOLOGY

The endemicity of HAV depends upon the hygienic and socioeconomic standards of a region. Hepatitis A has a higher sporadic and endemic rate than all other types of hepatitis. Around the globe, millions of cases are reported, and thousands of people die annually due to hepatitis A. Its prevalence rate is higher in low-income countries than in developed countries (Jacobsen 2018). Its illness rate over the years is described in Fig. 6 (CDC 2020). Hepatitis A infected countries and regions can be classified into high, intermediate, low, and very low HAV endemicity presenting areas as shown in Fig. 7.

5.1. HIGH ENDEMICITY

The high incidence of HAV persists in most developing countries. The highest infection rate of HAV occurs in regions with the lowest living standards. Hyperendemic countries are in African (Sub-Saharan) and

South Asian regions (Jacobsen 2018). Pakistan is also one of the highly infected countries with hepatitis A. Although these regions have a high rate of hepatitis, the surveillance of reported cases is very low due to the asymptomatic behavior of local populations. However, this asymptomatic illness confers even long-term immunity to infected patients. Seroprevalence survey in high endemicity regions shows that nearly 100% of adults and older children have IgG (anti-HAV immunoglobulin) levels in their blood, indicating past viral exposure. These statistics provide evidence of the high incidence rate and adaptive immunity of individuals in low-income countries (Jacobsen 2009).

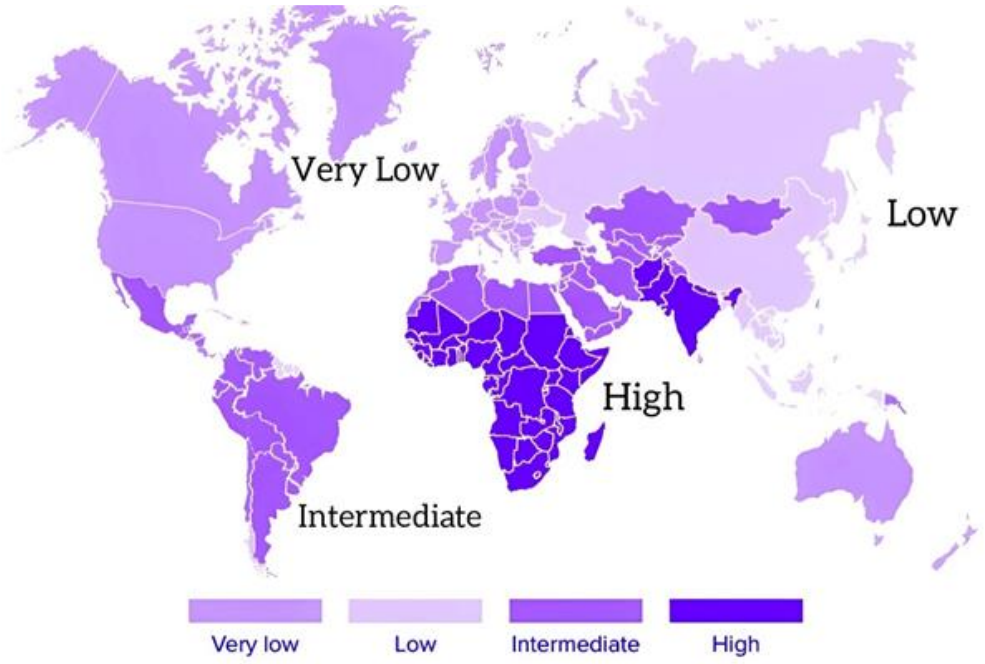

Fig. 7: Worldwide map of HAV seroprevalence (Retrieved from Paintmap)

5.2. INTERMEDIATE ENDEMICITY

These regions have a medium level of hepatitis A incidence. The sanitation and hygienic conditions are improved to facilitate the individuals and decrease the HAV incidence rate; however, populations are still susceptible to HAV due to the low vaccinations and immunity development. Eastern Europe, Middle Asia, and South American countries are on the hit list of intermediate incidences of HAV (Jacobsen and Koopman 2004).

5.3. LOW ENDEMICITY

These areas have a relatively low incidence rate of HAV, primarily due to vaccination efforts, improved hygienic norms, and better sanitation. HAV infection is unusual in these regions and often invades individuals during traveling or immigration from high or intermediate-susceptible countries. East Asian and East European regions mainly include in this category (Jacobsen and Wiersma 2010).

5.4. VERY LOW ENDEMICITY

These regions have a minimal incidence of HAV. Viral infection is sporadic due to universal vaccination, advanced research, high hygienic measures, and promising sanitation. Although these regions have a

negligible rate of HAV, very severe cases of HAV-infected children and adults have been reported due to less innate immunity and local exposure to this virus. That's why many adults and children remain susceptible to this disease (Carrillo-Santisteve et al. 2017). Australia, North America, and Western Europe fall in this category (Koff 2004).

6. ZOONOTIC FACET

Hepatitis A is a host-limited viral disease that principally affects humans. Unlike hepatitis E, it does not have a wide range of infected host transmission; however, there are some instances where it has been transmitted from animals to humans and holds zoonotic importance. The main animals implicated in the zoonosis of hepatitis A are non-human primates, i.e., new-world monkeys, old-world monkeys, and Apes (Lanford et al. 2019). The zoonotic relevance of hepatitis A is very uncommon and is associated with close contact between humans and infected animals. These animals carry and shed the virus in their feces. Humans get this infection from animals related to their life activities. People who toil directly with these primates, such as veterinarians, researchers, animal handlers, and zookeepers, are at a high risk of acquiring zoonotic infection (Smith et al. 2017).

These non-human primates share genetic relevancy with human DNA; thus, pathological sequences of the viral infection in hepatocytes are similar in these primates as in humans. Zoonotic transmission of HAV has significant importance in low-income countries due to the typical habitat of humans living with these primates. In developed countries, it has zoonotic significance because biomedical research centers and zoos provide direct exposure to these primates. Seafood also plays a crucial role in zoonotic complications of hepatitis A (Halliday et al. 1991; Pintó et al. 2009). In China, bivalve shellfish, i.e., oysters, cockles, and calms, are a leading cause of HAV transmission to the human population. Shellfish are filter feeders that can live in contaminated water and concentrate the virus in their bodies. Thus, shellfish eating causes the infection of hepatitis A in humans (Xu 1992; CFS 2000). The susceptibility of HAV in mice with some genetic depletion and modification in the virion has also been observed. The basic theme of this study was permitting experimental broadness of the host range, zoonotic mode, and interferon-mediated responses on viral prevalence (Hirai-Yuki et al. 2018).

7. CLINICAL SIGNS AND SYMPTOMS

HAV has a broad range of clinical manifestations, from severe liver damage to mild instances of disease with no signs and symptoms. Clinical interventions are mainly dependent upon the age of the infected patient. In children under 6 years of age, HAV usually remains asymptomatic, and illness remains anicteric, but in adults, it is symptomatic in 70% of cases (Hadler et al. 1980; Abutaleb and Kottilil 2020). There are two types of clinical manifestations based on the duration of the illness.

7.1. TYPICAL MANIFESTATIONS

It includes the prodromal and icteric phase symptoms of the disease that start after the incubation period of HAV, about one-month following exposure to the viral attack (Fig. 8). The prodromal phase includes the very first nonspecific symptoms of HAV that last for 5-7 days. This phase is the onset of cytopathic effects in the liver, resulting in the initial change in the body functions. Fever, anorexia, fatigue, malaise, and vomiting are the common complaints of adults during the prodromal phase of HAV infection, but small children usually don't show any such signs or symptoms (Martin and Lemon 2006; Van Damme 2017).

The icteric phase starts after the prodromal phase. It is the severe stage of hepatitis A and has clinical importance due to the jaundice manifestation. During the icteric phase, there is inflammation of the liver

due to immune-mediated attacks on the hepatic cells. The hepatocytes become dysfunctional, and their structure changes leading to hepatocellular injury. This inflammation disrupts the breakdown of red blood cells and produces nonconjugated bilirubin. Jaundice is characterized by the paleness (yellowing) of the skin, especially on the hands and feet, sclera of the eyes (icterus), and mucous membranes of the body due to the accumulation of bilirubin in these tissues (Hoofnagle and Seeff 2006; Dienstag 2019). Accumulation of conjugated bilirubin in the kidney also leads to dark urine production during the very onset of this phase. ALT and AST levels increase in serum due to hepatic dysfunction and inflammation. There is severe upper right-quadrant abdominal pain due to hepatomegaly (inflamed liver). Less common symptoms include diarrhea, skin rashes, and pruritis, which may also appear during the icteric phase (Khan et al. 2012).

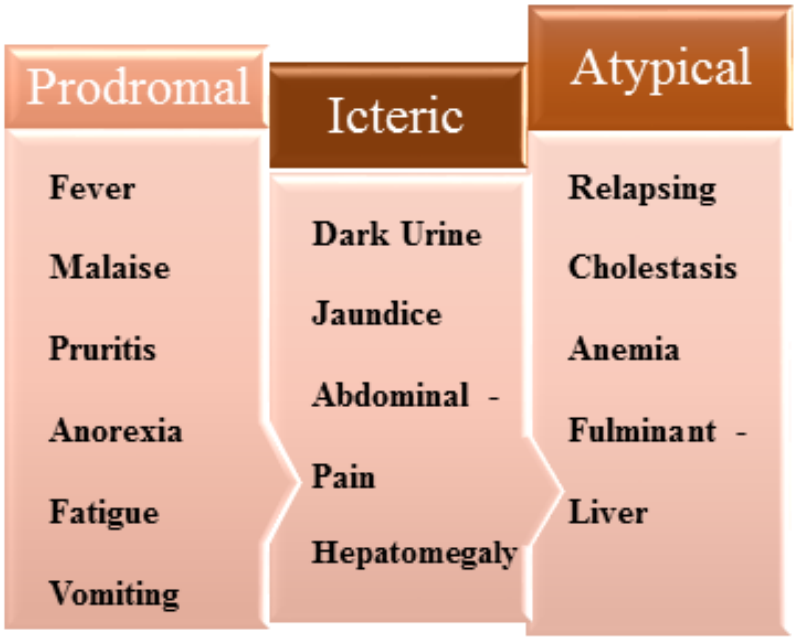

Fig. 8: Symptoms of HAV during the initial and late stages of infection

7.2. ATYPICAL MANIFESTATIONS

HAV cannot establish long-persistent infection in humans or non-human primates and cannot induce chronic infection even in significantly immunocompromised patients. It is a self-limited disease and does not prolong to chronicity. Typically, the illness persists for less than 2 months; however, many atypical complications can occur in 10 to 15% of the patients. These symptoms include relapsing hepatitis, prolonged cholestasis, acute liver failure (fulminant liver failure), and other extrahepatic manifestations (Jeong and Lee 2010). Relapse of disease occurs after 2 to 6 months of the initial viremia, but it does not cause such a severe form of hepatitis as the initial one accomplishes (Glikson et al. 1992).

Prolonged cholestasis (accumulation of bile elements in the liver) causes the impairment of bile flow and lasts up to 6 months, resulting in intense pruritis, malabsorption, and fatigue (Sherman 2015). The severe form of hepatitis A is fulminant hepatitis, characterized by the rapid progression of liver failure. Fulminant hepatitis occurs in less than 1% of HAV-infected patients. The risk of fulminant hepatic failure is more targeted in adults over 40 years of age with chronic liver disorders (Murphy et al. 2016). It develops in scarce situations of HAV but is potentially characterized by life-threatening complications. Higher viral concentrations in aged patients cause viremia that is impatient to recover

due to immunosuppression, ultimately leading to acute hepatic failure (Lee et al. 2015; Moon et al. 2018). It has a high mortality rate, and a liver transplant can be the only option for survival (Uchida et al. 2018).

8. HAV DIAGNOSIS

HAV infection cannot be clinically diagnosed because it may include similar reaction symptoms to other types of hepatitis. Due to the single serotype, detection of the anti-HAV antibodies in the blood is very easy. It can be differentiated from other types of hepatitis by examining the humoral immune response of the patient's body. These antibodies are detected by serological testing. There are different techniques to determine HAV positivity in the infected patient (Tennant and Post 2016; Medscape 2021).

8.1. ANTIBODIES EXAMINATION

In this method, IgM antibodies against hepatitis A are examined (Park et al. 2009). IgM antibodies mainly detect the capsid proteins of HAV. These antibodies start proliferating about 1-2 weeks after exposure to infection and persist for several months. Before the onset of clinical symptoms, anti-HAV IgM antibodies start proliferating in the blood. However, IgM levels can report false results due to autoimmune hepatitis or rheumatoid factors, which cause cross-reactivity of antibodies. Therefore, it is not advisable to rely only upon this antibody detection test (Lee et al. 2013; Tennant and Post 2016).
After one week of IgM production, IgG antibodies produce in the convalescent period of infection and persist in the body for the whole life to secure a person against relapsing of the infection (Fig. 9). IgG antibodies remain in feces, urine, serum, and saliva even post-exposure to the disease (Chitambar and Chadha 2000; Oba et al. 2000). Enzyme-linked immunosorbent assay (ELISA) is preferable to distinguish between IgM and IgG antibodies in the blood. The comparison between these two antibiotics gives enough data to detect the previous infection or ongoing viremia in the patient's body (Crum-Cianflone et al. 2011). These antibodies can be easily collected from saliva and used for anti-HAV saliva analysis. Saliva examination is more feasible in outbreaks and epidemiological testing due to the simplicity of sample collection from a large number of individuals (Augustine et al. 2020).

8.2. LIVER ENZYMES EXAMINATION

HAV causes liver inflammation, which results in elevated levels of several enzymes, i.e., alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and aspartate aminotransferase (AST). Their level becomes 5-50 times increased in the blood. This test indicates the infection complexity during the onset of HAV symptoms. Increased level of these enzymes in the blood helps to measure the infection rate of the liver by comparing it with standard enzyme values (Medscape 2021).

8.3. ANTIGEN EXAMINATION

The nucleic acid of HAV is detected in the infected samples of patients through Nucleic acid testing (NAT). It is the more sensitive and accurate method for examination. This technique includes Southern blotting (Buti et al. 2001; Calder et al. 2003), single-strand conformational polymorphism (Goswami et al. 1997; Fujiwara et al. 2000), real-time PCR (Costa-Mattioli et al. 2002) and reverse transcription-PCR (Polish et al. 1999; Cromeans et al. 2001). The most sensitive, precise, and extensively used method for HAV-RNA detection is RT-PCR. This method is a low-cost HAV detection test with the gold standard of specificity (Kozak et al. 2022).

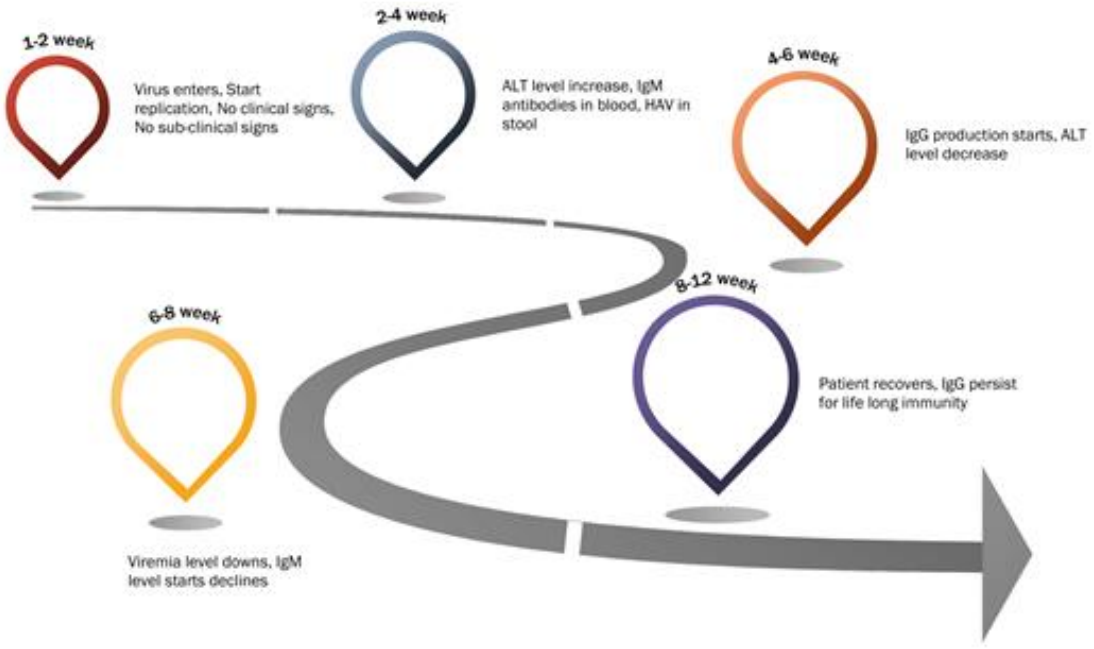

Fig. 9: Antibodies production sequence and their levels in the body after exposure to the HAV

9. TREATMENT & PREVENTION

Hepatitis A has no specific treatment. The infected patient is given supportive treatment against the disease. In most cases, patients recover on their own without any medication or assistance. Proper rest is required to conserve body energy during the acute stage of illness. Fresh water and juices are recommended to maintain the body's electrolytes during vomiting and diarrhea. Antiemetics and antipyretics can be used to control vomiting and fever (Lanford et al. 2011). In fulminant hepatitis, hospitalization is required for proper monitoring of liver functions and supportive therapy. Anti-viral drugs are used briefly, but it is advisable to refrain from any drug intake during the acute phase of HAV (Migueres et al. 2021). Recovery usually takes 3-7 weeks. Auxiliary care and better nutritional therapy are effective for treatment. Interferon treatment for acute hepatitis was previously effective in some HAV-infected patients, but results remained limited and unclear (Crance et al. 1995). Further quality research is required to investigate and discover suitable medication against HAV.

Complete sanitation and self-hygiene, such as regular handwashing, sanitizing hands before meals and after using the toilet, proper vaccination, proper cooking of food at high temperatures, water chlorination, and use of disposable plates or glasses on public water and food courts, can help to prevent the HAV infection. Preventive techniques for the sexual transmission of HAV should be adopted using safe sex methods (Ndumbi et al. 2018). Despite vaccination availability, a challenge to developing anti-viral treatment still has space to discover more in this field to shorten the period of symptoms, limit the outbreaks, reduce drug ineffectiveness, and treat atypical complications like fulminant liver (Thomas et al. 2012; Migueres et al. 2021).

9.1. PASSIVE IMMUNIZATION

Passive immunization against HAV is provided to the infected patient by administering immunoglobin. It provides the immediate source of antibodies against HAV. Immune globulin is recommended in patients

with severe HAV infection. It is provided as a post-exposure prophylaxis to immunocompromised patients, the elderly, and patients with chronic liver diseases. In the modern era, immune globulin is now being replaced by inactivated vaccines due to its short time action and large dose requirement (Victor et al. 2007).

9.2. ACTIVE IMMUNIZATION / VACCINATION

Vaccination in the whole community is a strategic approach toward eliminating and preventing the hepatitis A virus (Bell and Feinstone 2004). Developed countries have adopted the universal vaccination program, resulting in the control of HAV. Two vaccine forms are available against HAV: live-attenuated and inactivated (Patterson et al. 2019). Inactivated vaccines are the most commonly used in developing and some developed countries. These are effective for pre-exposure prophylaxis but require multiple doses over time to obtain ongoing HAV immunity. In China, an attenuated vaccine against HAV has been developed with a weekend virus form and provides long-lasting immunity than inactivated vaccine (WHO 2019). Vaccines have several advantages over immune globulin, including long-term immunity, pre-exposure prophylaxis, and easy availability in market. Usually, two main doses of the HAV vaccine are administered to individuals. The first dose is given after 1 year, and the second booster dose is given after 6 months following the first dose. Routine vaccines with an additional single dose are provided against HAV before international traveling, patients with chronic liver failure, HIV-infected patients, and people who use injection drugs (CDC 2021).

10. CONCLUSIONS

Hepatitis A has the most viremic prevalence among all other forms of hepatitis. It is a pervasive disease of humans, which has become a global curse affecting developed and developing countries every year. The primary mode of person-to-person transmission of HAV has more importance than its zoonotic mode of animal-to-human transmission. However, its zoonotic aspects highlight the need for precautions and safety measures to follow while handling and working with these animals. Personal hygiene, proper nutritional equipoise, along with immunization are the best strategies to adopt during incipient and prophylactic cures against this disease.

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