Transmission, Pathology, and Prevention Strategies of Hepatitis A Virus

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Abstract Hepatitis A virus (HAV), a gastrointestinal virus primarily transmitted through food and water sources, poses a significant threat to global public health. HAV is mainly spread through the fecal-oral route, and transmission occurs in environments with contaminated food, unsafe drinking water, and poor sanitation. HAV infection damages liver cells and leads to a range of clinical symptoms, including jaundice, nausea, and fatigue. Prevention and control strategies for hepatitis A mainly encompass vaccination, health education, and improving environmental hygiene. Additionally, considering the distribution of HAV genotypes, tailored prevention and control strategies are necessary for different regions and populations. This review article aims to systematically summarize the transmission routes, pathological characteristics, and prevention strategies of HAV. It contributes to a deeper understanding of HAV transmission, pathological mechanisms, and multi-layered preventive measures, thus providing a scientific foundation for raising public awareness and strengthening disease prevention and control.

Keywords Hepatitis A virus; Transmission routes; Pathological characteristics; Prevention strategies; Public health

Hepatitis A Virus (HAV) is a small RNA virus belonging to the Hepatovirus genus. The genetic material of HAV consists of a single-stranded positive-sense RNA genome containing around 7 500 nucleotides (Wang et al., 2015). The viral particles have a diameter of approximately 27 to 32 nanometers and exhibit an icosahedral symmetrical spherical shape (Figure 1) (Lemon et al., 2018). HAV is the only known virus capable of causing acute viral hepatitis in humans.
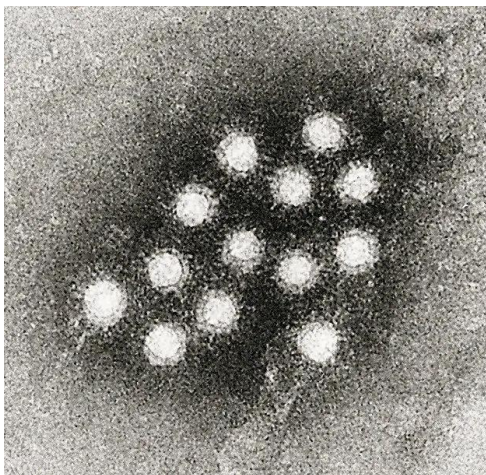

Figure 1 Hepatitis A virus under electron microscope

HAV is primarily transmitted through the fecal-oral route, which involves the ingestion of contaminated food or water leading to infection. Within the intestines of infected individuals, the virus undergoes substantial replication and is subsequently excreted through feces. Consequently, unclean food, water, and contact with contaminated objects can all serve as pathways for HAV transmission. Additionally, close contact with infected individuals, especially among household members and caregivers, can also contribute to the spread of hepatitis A.

Infection with HAV typically leads to acute hepatitis, characterized by symptoms such as fatigue, loss of appetite, nausea, vomiting, and jaundice. Most patients recover within several weeks after infection, and the disease usually does not progress to chronic hepatitis. However, individuals who are younger in age or have compromised immune systems might experience severe symptoms, potentially leading to liver failure.

Due to the transmission routes of HAV and the characteristics of high-risk populations, controlling the spread of hepatitis A is crucial for public health. Vaccination is an effective measure in preventing hepatitis A and has been widely implemented in many countries. Additionally, improving sanitation, enhancing health education, and strengthening case monitoring are important steps in controlling HAV transmission. A thorough understanding of the transmission pathways and infection mechanisms of HAV aids in formulating more effective prevention and control strategies, reducing the risk of outbreaks and dissemination (Jacobsen and Koopman, 2005). Investigating the liver pathology changes caused by HAV infection can deepen our understanding of liver diseases, providing new insights for treatment and prevention (Kanda et al., 2017). Research into the immunological characteristics of HAV and vaccine development contributes to enhancing population immunity against hepatitis A, effectively controlling the spread and prevalence of the virus.

In recent years, significant progress has been made in the research on HAV, yet certain mysteries remain unresolved, such as immune evasion mechanisms and potential chronic infections. This review aims to comprehensively summarize and consolidate the transmission, pathology, and prevention strategies of HAV, offering the latest research advancements for a deeper understanding of the etiology, pathology, and epidemiology of hepatitis A. Furthermore, it provides a scientific basis for the development of more effective prevention and control strategies and the creation of novel vaccines.

1 Overview of Hepatitis A Virus
1.1 Structural characteristics of Hepatitis A virus
The viral particles of HAV consist of four main structural proteins: VP1, VP2, VP3, and VP4 (Figure 2). Among these, VP1 is the primary capsid protein, constituting 60% of the viral particle. It determines the virus's antigenicity and immunological properties. VP2 and VP3, on the other hand, are minor structural proteins involved in the assembly of the viral particle (Wang et al., 2015). In contrast, VP4 is located inside the viral particle, and its function in HAV is not yet fully understood.
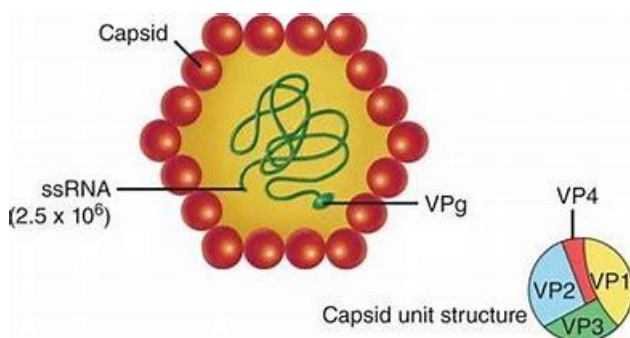
Figure 2 Structure of Hepatitis A virus

Based on phylogenetic analysis of the full-length VP1 sequence, HAV is classified into six genotypes, designated as genotypes I to VI. Among them, genotypes I to III primarily infect humans. These genotypes are further divided into subtypes A and B, denoted as IA, IB, IIA, IIB, IIIA, and IIIB. On the other hand, genotypes IV to VI are mainly found in animals such as primates.

The structural protein VP1 of HAV is also involved in binding to the host cell receptor, mediating the process of virus entry into host cells. The receptor for HAV has been identified as TIM-1 (T-cell immunoglobulin and mucin

domain-1). Furthermore, research has indicated that there might be other interactions between HAV and host cells, including interactions with intracellular RNA-binding proteins and signaling pathways.

The genome of HAV is composed of a single-stranded positive-sense RNA containing 7 500 nucleotides. The 5' end of the RNA is linked to the viral genome-linked protein (VPg) or 3B. At the 3' end of the genome, there's a lack of a typical cap structure and a short untranslated region, instead being terminated with a poly(A) tail. The genome encodes a large polyprotein, and its translation is regulated by an internal ribosome entry site (IRES). There are two non-coding regions at the 5' and 3' ends of the HAV genome.

Structural proteins are translated from the P1 region, while non-structural proteins involved in virus replication are encoded in the P2 and P3 regions. The viral capsid is composed of 60 capsomers, displaying HAV-specific antigens, leading to the presence of a single serotype in human HAV. Each capsomer consists of four proteins (VP1, VP2, VP3, and VP4) and seven non-structural peptides (2A, 2B, 2C, 3A, 3B, 3C, 3D).

According to the study by Khudyakov et al. (1999), they utilized 237 overlapping synthetic peptides of 20 amino acids each (covering all HAV proteins) and reacted them with a series of acute HAV sera. This analysis revealed 42 antigenic sites. Among these, 5 were identified as immunodominant regions. The first immunodominant region spans amino acids 57 to 90 and includes the VP2 protein. The second region, located at amino acids 767 to 842, encompasses the entire P2A protein and a portion of the VP1 protein. The third region, from amino acids 1 403 to 1 456, involves the C-terminal of the P2C protein and the N-terminal of P3A. The fourth region, spanning amino acids 1 500 to 1 519, encompasses almost the entire P3B protein. The final region, located at amino acids 1 719 to 1 764, includes the C-terminal of the P3C protein and the N-terminal of the P3D protein.

1.2 Genetic characteristics of Hepatitis A virus

The genetic characteristics of HAV exhibit a relatively stable pattern worldwide, with a relatively low degree of nucleotide sequence variation. However, there might be some degree of variation among HAV strains from different regions and time periods. These variations typically occur in the coding regions of non-structural proteins and could potentially impact the virus's biological properties and pathological manifestations.

Recent research has identified that HAV strains from various global regions can be categorized into six distinct genotypes, namely genotypes I to VI. Different genotypes of HAV exhibit differences in certain gene segments. Studies indicate that genotypes I and III of HAV are the most widely spread globally, while other genotypes are more commonly found in specific regions or at particular time points (Wu et al., 2020).

Different genotypes of HAV may be associated with distinct epidemiological characteristics and clinical manifestations in different regions. For instance, genotype I HAV primarily spreads in developing countries, often linked to contaminated food and water sources, leading to larger-scale outbreaks. On the other hand, genotype III HAV is more common in developed countries, predominantly transmitted through close contact, with milder clinical symptoms. Additionally, research has revealed a certain degree of correlation between genetic distances among genotypes and geographical distances. This suggests that the spread of HAV might be influenced by geographical factors.

Genetic variations in HAV also play a role in vaccine development and vaccine efficacy. Due to differences among genotypes, current hepatitis A vaccines are primarily based on genotype I HAV, potentially having limitations in coverage for other genotypes. Therefore, vaccine development needs to take into consideration the characteristics of different regions and genotypes to achieve effective prevention and control of hepatitis A on a global scale.

In-depth research into the genetic characteristics of HAV contributes to a better understanding of the virus's patterns of transmission, vaccine development, as well as differences in epidemiological and pathological manifestations. This research provides a scientific foundation for the prevention and control of hepatitis A.

1.3 Invasion of Hepatitis A virus

The process of HAV invasion is a crucial step in viral infection and marks the starting point for host cell responses and disease development. Research indicates that the invasion mechanism of HAV involves interactions between multiple molecules and cytokines. These interactions play a significant role in regulating both the virus's entry and the host immune response.

In general, the invasion process of HAV can be divided into the following stages: adsorption, internalization, and release. During the adsorption stage, HAV binds to host cell surface receptors, allowing the viral particles to come into close contact with the cells. These receptors might include specific molecules on the surface of liver cells, such as TIM-1 (T-cell immunoglobulin and mucin domain-1). Research has also revealed that the adsorption of HAV can be influenced by the physiological state of the cell and the environment, including factors like the lipid composition of the cell membrane.

After adsorption, HAV is internalized into host cells. This process may involve both endocytosis and phagocytosis by the cell. Following internalization, viral particles of HAV are enveloped in cell membrane vesicles, forming endosomes. Research suggests that the internalization of HAV is associated with certain cellular protein factors such as Clathrin and Dynamin. These factors participate in the formation of endocytic vesicles and membrane fusion.

Lastly, within the endocytic vesicles, HAV may release its viral genome, initiating the infection of the host cell. During this stage, the genome of HAV might be released into the cytoplasm, and subsequently enter the cell nucleus through nuclear pores, enabling viral replication and production to commence

1.4 Intracellular replication of Hepatitis A virus

While the detailed mechanisms of HAV entry into host cells are not completely clear, research has proposed that gangliosides might be one of the key molecules facilitating HAV entry into host cells (Das et al., 2020). Gangliosides allow HAV particles to escape lysosomes. Moreover, unlike the smooth capsids of viruses like foot-and-mouth disease virus, and the major depressions (canyons) at the five-fold symmetry axes of enteroviruses like poliovirus, the surface of HAV capsid lacks such features as potential receptor binding sites due to the absence of canyons.

HAV replicates within the liver and penetrates host cells by interacting with cell surface molecules, particularly sialic acid and gangliosides. The virus then sheds its viral RNA from the endosome and transfers it into the cytoplasm. Supervised by the internal ribosome entry site (IRES), the viral polyprotein is synthesized into various structural and non-structural proteins. Subsequently, HAV utilizes cell membrane-derived structures resembling organelles to replicate its genome within them. Once the newly synthesized genome is packaged, the newly formed HAV particles leave the cell in a quasi-enveloped state (Figure 3), released into the biliary tree. The detergent properties of bile acids cause eHAV to lose its envelope near the proximal biliary system, resulting in non-enveloped virus particles passing through the intestine and being excreted from the host in the feces.

On the basolateral membrane of liver cells, HAV interacts with host cell receptors, and its non-enveloped RNA is released into the cytoplasm. The positive-sense RNA genome is translated through cap-dependent mechanisms and IRES-driven translation, generating a variety of proteins. Non-structural proteins (2B, 2C, 3AB, 3Dpol), protease (3Cpro), and capsid proteins undergo multi-step proteolytic processing. The 2BC protein induces changes in intracellular membranes, leading to the formation of membrane-bound replication enzyme complexes. This complex guides the production of complementary negative-strand RNA, which serves as a template for generating multiple new copies of the RNA genome. The newly synthesized positive-strand RNA can further guide translation, RNA biosynthesis, or be packaged into capsids, forming intracellular virus progeny.

These newly formed viral components are encapsulated into multivesicular bodies, eventually entering either the bile canaliculi or the liver sinusoids through the apical plasma membrane and basolateral plasma membrane, respectively. Upon entry into the cell, the RNA genome is exposed and engages with host ribosomes, forming polyribosomes. The viral RNA polymerase is used for translation and the synthesis of viral particles, which can be assembled and released into the biliary system.
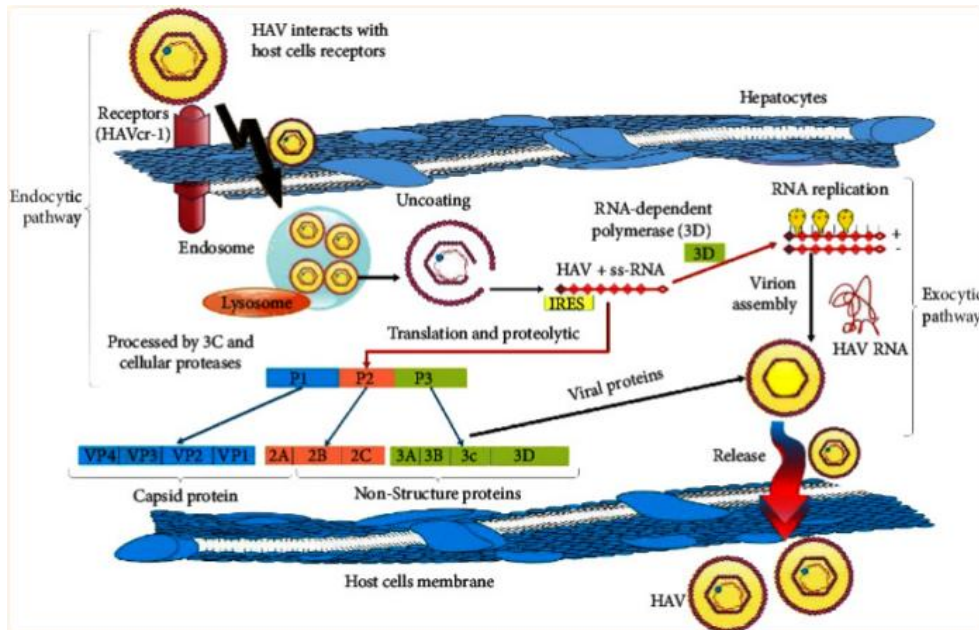

Figure 3 Replication cycle of HAV

1.5 Spread of Hepatitis A virus

HAV, as a non-enveloped small RNA virus, possesses unique survival characteristics that allow it to remain relatively stable in the environment. This differs from other small RNA viruses. These properties present challenges for the prevention and control of hepatitis A, emphasizing the importance of formulating scientifically effective control strategies.

HAV can survive in the environment without a host. Once excreted into the environment, such as in the feces of an infected individual, HAV can maintain its survival independently of host cells (Schillie et al., 2020). This ability allows HAV to remain relatively stable in the environment for a certain period of time within the transmission pathways.

HAV demonstrates strong resistance to acidity and low temperatures. When attached to inorganic or organic matter, HAV exhibits a certain level of resistance to acidic conditions and cold environments. This enables HAV to survive in contaminated food or water sources. In some cases, HAV can even survive on the surface of food or objects in contact with food for several weeks.

Due to HAV's high ability to survive outside the host, its transmission pathways are relatively broad. It primarily spreads through the fecal-oral route but can also be transmitted through the consumption of contaminated food or water, as well as close person-to-person contact. In areas with poor sanitation and among specific populations, outbreaks and transmission of hepatitis A are more likely to occur, emphasizing the significance of these transmission routes.

Strengthening food safety, ensuring the hygiene of drinking water sources, and enhancing the cleaning and disinfection of environmental objects contaminated with the virus are all crucial measures for effectively

preventing the spread of HAV. Furthermore, intensifying public health education, particularly regarding personal hygiene and food safety, is a key step in breaking the chain of HAV transmission.

2 Hepatitis A Infection

Hepatitis A, caused by the hepatitis A virus (HAV), is an acute infectious disease. It generally presents as an acute illness and does not progress to chronicity. The infection is self-limiting, typically resolving within 4 to 7 weeks, and has no long-term effects. Unlike hepatitis B and C viruses, HAV does not appear to cause persistent liver damage. The incubation period of hepatitis A ranges from 2 to 6 weeks, with an average of 4 weeks. It's important to note that HAV has a very high transmission efficiency, even in developed regions with good hygiene conditions and personal habits. Close contacts of hepatitis A patients, including family members, have a relatively high infection rate (25%~50%).

2.1 Clinical symptoms of Hepatitis A

Patients with hepatitis A often exhibit a wide range of clinical symptoms. The disease has a relatively high hospitalization and mortality rate. According to reports from the Centers for Disease Control and Prevention (CDC), the distribution of HAV infection rates varies significantly across different age groups (Table 1). The clinical symptoms also differ based on the age of the patients, showing a trend from mild to severe. Infection during childhood often results in asymptomatic cases, while in adults, hepatitis A frequently presents with typical symptoms of acute hepatitis, such as jaundice, fatigue, and general weakness.

Table 1 Distribution rate of HAV per 100 000 people grouped by age

Age	Years				
	2016	2017	2018	2019	2020
0~19	0.4	0.3	0.7	0.9	0.3
20~39	1.8	3.5	15.9	22.4	10.9
40~59	1.5	2.7	10.1	16.6	9.5
≥60	0.6	0.7	1.4	2.3	1.4

In some cases of childhood HAV infection, individuals may experience asymptomatic infection, where patients do not exhibit noticeable clinical symptoms but still carry the virus and can transmit it to others. After HAV infection in adults, the majority of cases manifest with typical symptoms of acute hepatitis, including jaundice (yellowing of the skin and eyes due to the accumulation of bilirubin resulting from liver cell damage), fatigue, general weakness, loss of appetite, nausea, and vomiting. Hepatitis A patients may also experience atypical accompanying symptoms such as headache, joint pain, muscle aches, and diarrhea.

A portion of adult patients may experience more severe symptoms, known as fulminant hepatitis, which has a higher incidence of occurrence. In severe cases, liver transplantation might be necessary. It has been reported that among individuals aged 50 and above, the mortality rate for fulminant hepatitis can be as high as 5.4%. Approximately 10% of patients may experience a recurrence of symptoms after recovery, leading to a prolonged disease duration of several weeks to months.

It's important to note that if a patient already has other chronic liver diseases, such as hepatitis B or hepatitis C, and becomes infected with HAV, the risk of developing and the mortality rate of hepatitis A may increase. Therefore, individuals with pre-existing chronic liver conditions should be particularly vigilant about the possibility of contracting hepatitis A.

2.2 Hepatitis A global epidemiology

Hepatitis A is a global public health concern, with millions of cases reported annually. The incidence of hepatitis A is particularly high in developing countries and regions. The World Health Organization (WHO) estimates that there are approximately 1.5 million clinical cases of hepatitis A worldwide each year.

However, the actual incidence of hepatitis A infections could be ten times higher. Many infected individuals may not exhibit obvious clinical symptoms or might only show mild symptoms, leading to under diagnosis and under reporting. This means that the actual number of infections could be significantly higher than the reported cases, resulting in a serious underestimation of the epidemic.

Hepatitis A has resulted in a certain number of deaths globally. According to data from the World Health Organization (WHO), in 2016, hepatitis A caused approximately 7,134 deaths, accounting for 0.5% of the total viral hepatitis-related deaths that year. Although hepatitis A tends to be self-limiting in the majority of patients, meaning most individuals will recover on their own after infection, severe complications can arise in certain high-risk populations. This includes elderly individuals, those with weakened immune systems, or individuals with underlying chronic liver diseases. In these cases, serious complications such as liver failure can occur, increasing the risk of death.

In many countries with low endemic, there are few or even no local circulating strains of hepatitis A virus. As a result, a significant number of unvaccinated adults may not have acquired hepatitis A antibodies through asymptomatic infections during their childhood. If HAV is introduced into susceptible populations in these areas, it has the potential to cause larger-scale outbreaks of hepatitis A, with more severe clinical symptoms in affected individuals.

For instance, the United States experienced a prolonged hepatitis A outbreak in 2016, characterized by person-to-person transmission. The most affected populations were intravenous drug users, homeless individuals, and men who have sex with men. In total, approximately 37,778 people were infected during this outbreak, and around 61% of patients required hospitalization. Tragically, the outbreak resulted in a significant death toll, with 354 individuals losing their lives.

Meanwhile, in low-endemic developed countries, there is growing concern within public health authorities about food borne hepatitis A transmission. Typically, such outbreaks are triggered by contaminated foods that are consumed without requiring heat treatment, such as seafood, fruits, vegetables, and agricultural products. Due to the rapid growth of the food and transportation industries, perishable goods are often exported from agriculturally less-developed countries to some developed countries. When these high-risk and susceptible populations in developed countries purchase and consume these products, it can lead to hepatitis A food borne transmission.

Moreover, these outbreaks often exhibit characteristics of both temporal and spatial dispersion due to the extended shelf life and widespread distribution of the implicated food items. Without timely detection and effective control measures, the transmission of hepatitis A can quickly expand. For instance, in the years 2013 to 2014, multiple European countries experienced a cross-border outbreak linked to frozen berries, which resulted in over 1589 confirmed cases of infection.

2.3 Hepatitis A epidemiology in China
During the period from 2004 to 2015, a total of 574 697 cases of hepatitis A were reported in China, with an average incidence rate of 3.62 per 100 000 population. Over the past decade, the incidence of hepatitis A in China has been consistently decreasing (Cao et al., 2021). This trend can be attributed to the continuous improvement of public health standards and the widespread vaccination of children against hepatitis A.

On one hand, the improvement in healthcare standards in China has led to strengthened regulation of food safety and drinking water quality, which has reduced the pathways for hepatitis A transmission. Additionally, better handling and treatment of contaminated food and water sources have contributed to a decreased risk of hepatitis A infection.

On the other hand, China has implemented a large-scale childhood vaccination program that includes hepatitis A vaccine as a part of routine immunizations. The vaccination coverage among eligible children is relatively high.

According to data from a survey conducted in 2014, the vaccination coverage rate for hepatitis A among eligible children in China reached 98.8%. The promotion of childhood vaccination helps to lower the risk of hepatitis A infection among children, consequently reducing the spread of hepatitis A.

With the improvement of China's economy and healthcare standards, the traditional role of infection sources has gradually shifted away from children. Opportunities for the broader community to become infected with HAV and acquire immunity have decreased. As a result, apart from childhood vaccination, other population groups often lack protection from hepatitis A antibodies. According to a survey conducted in Shandong Province in 2015, the levels of anti-hepatitis A virus antibodies were below 85% for both the 12~24 age group and the 25~34 age group. Furthermore, a study in Shanghai in 2012 indicated that only 34.4% of individuals in the 20~24 age group had hepatitis A antibodies.

These data indicate that despite the significant success of childhood vaccination, there is still inadequate immune protection against hepatitis A in the adult population, particularly among adolescents and young adults. This emphasizes the need to enhance awareness and prevention efforts among other population groups, increasing their understanding of hepatitis A and its risks. Furthermore, for high-risk groups such as healthcare workers, food handlers, and travelers, vaccination might be considered to enhance immune protection.

2.4 Coinfections in Hepatitis A

Due to similar modes of transmission, co-infection with hepatitis A virus (HAV) and hepatitis E virus (HEV) is quite common. Jaundice, fever, fatigue, and hepatomegaly are common clinical manifestations of combined infections involving hepatitis A, hepatitis E, and acute viral hepatitis. Dual infection can lead to severe complications and an increased risk of mortality, particularly due to the heightened risk of acute liver failure in both children and adults.

A recent study from India reported a co-infection rate of approximately 6% for HEV and HAV (Murhekar et al., 2018). Another study from Bangladesh indicated a dual infection rate of about 5.3% (Sayed, 2023). From 2006 to 2020, there has been a decline in the co-infection rate, which may be attributed to the high vaccination coverage for hepatitis A and improvements in hygiene conditions.

Researchers have found that the proportion of individuals co-infected with hepatitis A virus (HAV), HIV, and syphilis is unexpectedly high. The seroprevalence of HAV infection in HIV-positive individuals is higher compared to HIV-negative patients. Significant global variations can be observed between countries with low and high endemicity of hepatitis A. Evidence suggests that the HAV seroprevalence is higher in the HIV community, which is associated with factors such as oral-anal sex, a higher number of sexual partners, advanced age, and injection drug use.

Furthermore, a large cohort study conducted in Taiwan found a correlation between syphilis infection and hepatitis A virus (HAV) infection during an HAV outbreak in HIV-positive individuals. Similarly, in a recent study of a hepatitis A outbreak in France, 54% of patients were diagnosed with at least one sexually transmitted disease (syphilis, chlamydia, and gonorrhea infections).

Some studies have also found cases of concurrent dengue virus infection in individuals with hepatitis A virus (HAV) who also had anti-HAV IgM antibodies. There have been reports describing cases where individuals partially recovered from HAV infection and later contracted dengue fever. Acute fulminant liver failure exacerbated their condition, and they succumbed to a fatal co-infection of dengue fever and HAV. In a reported case from Karnataka, India by Bhat et al. in 2016, a 16-year-old boy was found to have concurrent infection of hepatitis A and dengue fever, resulting in significant changes in his liver function. Yakoob et al. also reported a case in Pakistan in 2011 where an individual had simultaneous infections of hepatitis A and hepatitis E viruses along with dengue fever.

3 Diagnosis of Hepatitis A

For individuals presenting with symptoms such as fever, fatigue, nausea, vomiting, abdominal bloating, and especially those with underlying risk factors such as lack of safe drinking water, drug use, cohabitation with hepatitis A patients, consumption of improper food and water, prompt medical evaluation and diagnosis should be sought once symptoms appear for timely treatment.

The diagnosis of hepatitis A relies on microbiological examination, primarily to determine the presence of hepatitis A virus (HAV) nucleic acid or antibodies in the patient's body. Currently, commonly used testing methods include polymerase chain reaction (PCR) for detecting viral nucleic acid, and immunological methods such as enzyme-linked immunosorbent assay (ELISA) for detecting antibodies.

In addition to microbiological tests, doctors also conduct a series of routine examinations to gather comprehensive diagnostic information. These examinations may include percussion of the liver area, ultrasonography (B-mode ultrasonography), complete blood count, urinalysis, and liver function tests, among others. These tests provide information about liver condition and function, aiding in the confirmation and assessment of the illness.

Early diagnosis is of paramount importance for timely intervention, preventing disease progression, and controlling transmission. Prevention and early treatment are crucial measures in controlling hepatitis A, aiming to minimize both infection and disease spread. Among high-risk populations, raising awareness and vigilance about hepatitis A, as well as conducting regular microbiological tests, are effective strategies to prevent the transmission of hepatitis A.

3.1 Microbiological examination

Microbiological examination is crucial for the diagnosis of hepatitis A, providing essential information for disease diagnosis, treatment, and prevention. There are three diagnostic criteria for confirming hepatitis A, with any one of them being sufficient for diagnosis:

Positive anti-HAV IgM (human anti-hepatitis A virus IgM antibody): During the acute phase, if a patient's blood tests positive for anti-HAV IgM antibodies, it indicates that the patient is currently experiencing an active hepatitis A infection. These antibodies typically appear within 2 to 3 weeks after infection and gradually diminish. Rapid tests (based on immunochromatography technology) can be used for antibody detection (Figure 4).
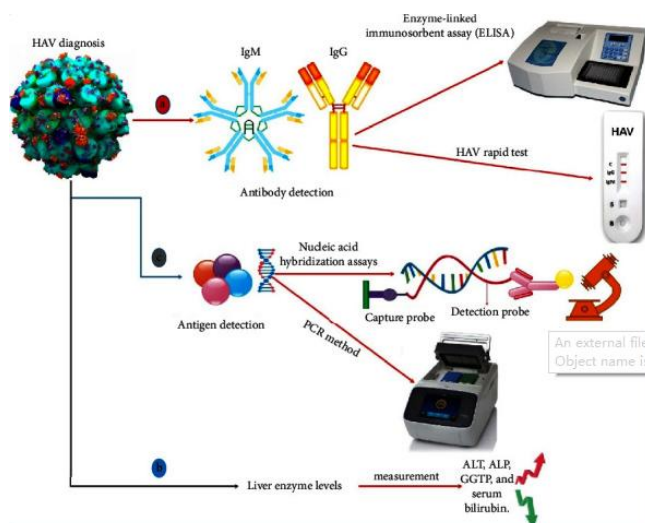

Figure 4 Diagnosis of Hepatitis A infection using different methods

Note: a: Specific diagnosis based on antibody detection, ELISA, and immunochromatography used for antibody differentiation; b: Examination of liver enzymes and serum bilirubin levels; c: Detection of viral genome using molecular methods like PCR

Positive anti-HAV IgG (human anti-hepatitis A virus IgG antibody): During the acute phase, anti-HAV IgG antibodies are typically negative, as it takes some time for IgG antibodies to develop. However, during the recovery phase, the levels of anti-HAV IgG antibodies in a patient's body gradually increase. The antibody titers during the recovery phase may be more than four times higher than those in the early phase, indicating a past hepatitis A infection and current recovery. During the recovery phase, anti-HAV IgM antibodies gradually decrease or disappear, while anti-HAV IgG antibodies persist and provide lifelong immunity. Elevated levels of IgG antibodies usually indicate that a patient has been previously infected with hepatitis A or has been vaccinated against it. Enzyme-linked immunosorbent assay (ELISA) is a common method for antibody detection. It can differentiate between anti-HAV IgM and anti-HAV IgG antibodies, helping doctors determine the stage of infection.

Direct detection of HAV RNA, HAV particles, or antigens in patient feces is the third criterion for confirming hepatitis A. This molecular detection method directly assesses the presence of the virus. Traditional HAV detection relies on a positive anti-HAV IgM serum test. However, research statistics indicate that 10~30% of patients might not be diagnosed through serology, especially in cases of early infection or low antibody titers. Direct molecular detection methods that identify viral nucleic acids, such as real-time polymerase chain reaction (PCR), could potentially enhance diagnostic accuracy (Figure 4).

Detecting viral nucleic acids or antigens can lead to earlier confirmation of infection, potentially allowing diagnosis even before symptoms manifest. This is crucial for implementing timely intervention measures, isolating patients, and preventing the spread of infection.

3.2 Clinical symptoms and signs

Patients with hepatitis A typically exhibit a variety of clinical symptoms and signs that hold significance in the diagnosis and assessment of the disease. Typical symptoms of hepatitis A include fever, fatigue, nausea, vomiting, and abdominal bloating. During the early stages of infection, patients might experience non-specific symptoms resembling a common cold or flu, making diagnosis potentially overlooked. It is particularly noteworthy that the symptoms and signs of hepatitis A vary across different age groups. Those infected during childhood often display asymptomatic infection or only mild symptoms such as fever and diarrhea. However, in adults, hepatitis A frequently presents with typical acute hepatitis symptoms, such as jaundice, fatigue, and generalized weakness.

Patients with hepatitis A often exhibit liver-related signs, especially tenderness and enlargement of the liver. Physicians can preliminarily assess whether the liver is abnormally enlarged by performing percussion on the liver area. This is a non-invasive examination method in which the physician gently taps or strikes the specific regions of the patient's abdomen using their fingers or a percussion hammer to observe and listen to the liver's sound and vibrations. If the liver is enlarged or has other abnormalities, there may be sounds different from normal or unusual vibrations felt during the examination.

Additionally, complete blood count (CBC), urinalysis, and liver function tests are important methods for evaluating liver damage. In the early stages of acute hepatitis, the total white blood cell count in the CBC is usually slightly elevated, which is due to the non-specific immune response triggered by the viral infection. During the jaundice phase, the total white blood cell count in the CBC returns to the normal range or may be slightly lower. At this point, the disease has progressed to the later stages, and the inflammatory response gradually subsides.

The main purpose of urinalysis is to assist in determining whether the patient's liver is damaged. In the early stages of hepatitis A, urinalysis can reveal an increase in urinary urobilinogen, which is one of the indicators of liver damage. As the disease progresses to the jaundice phase, urinalysis and blood tests often show significantly elevated levels of urobilinogen and bilirubin in the urine. Jaundice is one of the most common symptoms in

hepatitis A patients, resulting from liver damage that impairs the normal excretion of bilirubin, causing its accumulation in the body.

Liver function tests include indicators such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and direct bilirubin (Figure 4). Abnormal liver function can indicate the extent of liver damage. In patients with hepatitis A, liver cell damage caused by viral invasion and immune reactions can lead to elevated levels of ALT and AST, resulting in an increase in total bilirubin (TBIL) and direct bilirubin (DBIL) levels, leading to the appearance of jaundice.

3.3 Imaging examinations

Imaging examinations play a significant role in the diagnosis and treatment of hepatitis A. Among these, commonly used imaging methods include B-mode ultrasonography (ultrasound) and computed tomography (CT) scans.

B-mode ultrasonography is a non-invasive imaging technique that uses ultrasound waves to visualize and assess the structure and morphology of the liver. In patients with hepatitis A, B-mode ultrasonography can provide information about the liver's size, shape, and density. Through this examination, doctors can make preliminary assessments regarding the presence of abnormalities in the liver, such as hepatomegaly or structural irregularities. Additionally, B-mode ultrasonography can also detect the accumulation of fluids within the body, such as ascites.

Another commonly used imaging method is computed tomography (CT), which is an advanced cross-sectional imaging technique. Through multiple X-ray scans, CT can generate detailed cross-sectional images of the liver. In patients with hepatitis A, CT can provide more detailed information about the liver's structure, morphology, and potential lesions or injuries. CT examinations can also be somewhat helpful in assessing the liver's functional status, such as the patency of the bile ducts. However, due to the radiation involved, doctors will decide whether to perform this type of examination based on the patient's specific circumstances and needs.

Through imaging examinations, doctors can obtain more comprehensive and detailed information about the liver condition of patients with hepatitis A. These examination results can assist doctors in making accurate diagnoses and selecting appropriate treatment plans, thereby guiding the patient's treatment and recovery more effectively. It's important to note that the results of imaging examinations need to be interpreted in conjunction with other clinical information to ensure the accuracy and effectiveness of the final diagnosis and treatment plan.

4 Hepatitis A Prevention and Treatment

4.1 Vaccination

Widespread vaccination against hepatitis A is a key strategy for preventing the disease. Hepatitis A vaccines are designed and manufactured based on the virus's surface antigens. They stimulate the immune system to produce specific antibodies, providing individuals with long-term immune protection. The goals of vaccination primarily include two aspects: firstly, reducing the risk of infection to decrease the spread of hepatitis A; secondly, alleviating the severity of the disease, especially among high-risk groups such as children and individuals with chronic liver disease.

Hepatitis A vaccines are available as monovalent and combination vaccines. The former contains only hepatitis A virus antigens, while the latter can be combined with other vaccines to enhance convenience of administration. Vaccination is generally divided into routine immunization and booster immunization. Routine immunization is administered during childhood, while booster immunization is given after a certain period to maintain the immune effect. When implementing vaccination, factors such as regional epidemiology, population characteristics, and vaccine accessibility need to be considered to ensure the effectiveness and comprehensiveness of the vaccination program.

Vaccination not only protects individuals from hepatitis A but also helps reduce the risk of community-wide outbreaks, thereby safeguarding public health. Therefore, when formulating and implementing vaccination policies, countries need to consider factors such as the local epidemiology, disease patterns, and healthcare resources. This ensures the development of scientifically sound vaccination strategies that maximize the prevention goals of hepatitis A.

4.2 Health education and environmental hygiene improvement

Health education and the improvement of environmental hygiene are essential measures for preventing the transmission of hepatitis A. Strengthening health education by educating the public about the modes of transmission, preventive methods, and hygiene practices related to hepatitis A can raise individual awareness of health and encourage positive behavioral habits, thereby reducing the risk of infection. Particularly in high-prevalence areas and among high-risk populations, conducting regular health education activities and enhancing health awareness can guide individuals to adopt proactive preventive measures, reducing the potential for infection.

Simultaneously, improving environmental hygiene is a crucial aspect of preventing the spread of hepatitis A. Enhancing water supply and sanitation facilities to ensure the safety and hygiene of drinking water sources can effectively prevent viral transmission through water sources. Additionally, proper disposal of wastewater, garbage, and the reduction of environmental pollution can lower the risk of hepatitis A outbreaks. In terms of food safety, strengthening food hygiene supervision and inspections to ensure the safety and hygiene of food can help reduce cases of transmission through food.

Measures such as heating food to a temperature of at least $85°C$ for at least 1 minute, treating contaminated water with chlorine, or using a bleach solution to clean contaminated surfaces can effectively eliminate hepatitis A virus (HAV). These measures can disrupt the virus's structure and activity, thereby reducing the risk of infection. Ensuring thorough cooking of food during processing can effectively kill the virus. Additionally, disinfecting water sources and maintaining environmental hygiene are important measures for preventing the spread of hepatitis A.

To effectively promote health education and improve environmental hygiene, the efforts of various stakeholders such as governments, health departments, and community organizations are required. Strengthening monitoring and reporting of outbreaks, promptly investigating epidemic outbreaks, and taking measures to control their spread are also vital aspects to ensure the effectiveness of health education and environmental hygiene improvement.

4.3 Symptomatic treatment and rehabilitation care

For patients who have already contracted hepatitis A, symptomatic treatment and rehabilitation care are crucial. When clinical symptoms appear, seeking medical attention promptly for pathogen testing and diagnosis is essential for formulating effective treatment plans. For most hepatitis A patients, the disease will resolve on its own. However, in some cases, especially severe ones, symptomatic treatment and care can significantly alleviate symptoms and promote recovery.

For hepatitis A patients, particularly those displaying symptoms such as jaundice, doctors may administer a series of symptomatic treatments. These treatments may involve controlling symptoms, maintaining adequate nutritional intake, balancing electrolytes, and using medication when necessary. Resting, proper diet, and avoiding unnecessary strain on the liver are also recommended. Throughout the treatment process, doctors closely monitor the patient's liver function, condition, and treatment outcomes, adjusting the treatment plan accordingly. Severe cases, such as fulminant hepatitis or patients with concomitant liver diseases, may require hospitalization and specialized medical care.

The goal of rehabilitation care is to help patients regain their physical strength and mitigate the impact of the disease on daily life. During treatment, doctors guide patients in appropriate rest and avoiding excessive fatigue while encouraging moderate physical activity to facilitate recovery. Furthermore, proper diet and nutritional intake are crucial aspects of rehabilitation, particularly during the recovery period, ensuring the body receives sufficient energy and nutrients to promote recovery.

5 Prospects

Research on the transmission and prevention of HAV has made significant progress over the past few decades; however, many challenges and unexplored areas still remain. With the continuous advancement of technology and deepening research efforts, the study and prevention of HAV continue to offer vast prospects and challenges. Through ongoing efforts and innovation, it is hopeful that a deeper understanding of the nature of this disease will be achieved, providing more effective means for preventing and controlling hepatitis A.

In-depth research on HAV, ranging from its virus structure and genetic characteristics to its interactions with host cells, still holds many unexplored territories. The application of new research technologies and methods will provide us with a deeper understanding and may uncover further details about HAV transmission and pathogenic mechanisms.

The development of hepatitis A vaccines will remain a crucial means for preventing and controlling the disease. While vaccines are already available, vaccination rates are still suboptimal in certain regions and populations. In the future, we can anticipate the development of more advanced and effective vaccines to enhance protection and coverage. Additionally, the optimization and promotion of vaccine administration strategies will also be an important direction.

With the increase in globalization and population mobility, the cross-border transmission of hepatitis A poses a new challenge. Hence, international cooperation and information sharing will become even more crucial. Establishing effective monitoring systems and response mechanisms, and strengthening collaboration on an international scale, will aid in early detection and containment of the spread of hepatitis A outbreaks.

As technology continues to advance, new diagnostic methods and treatment strategies may emerge. The ongoing development of molecular diagnostic techniques could provide more sensitive and accurate approaches for early hepatitis A diagnosis. Additionally, there is potential for further research and development of therapeutic drugs and interventions specific to hepatitis A, offering improved treatment options for patients.

Author's contributions

Jianhui Li is the principal investigator of this study, responsible for literature collection, organization, article writing, and revisions. The author has read and approved the final manuscript.

References

Cao G., Jing W., Liu J., and Liu M., 2021, The global trends and regional differences in incidence and mortality of hepatitis A from 1990 to 2019 and implications for its prevention, Hepatology international, 15(5): 1068-1082.
https://doi.org/10.1007/s12072-021-10232-4

Das A., Barrientos R., Shiota T., Madigan V., Misumi I., McKnight K.L., Sun L., Li Z., Meganck R.M., Li Y., Kaluzna E., Asokan A., Whitmire J.K., Kapustina M., Zhang Q., and Lemon S.M., 2020, Gangliosides are essential endosomal receptors for quasi-enveloped and naked hepatitis A virus, Nature microbiology, 5(9): 1069-1078.
https://doi.org/10.1038/s41564-020-0727-8

Jacobsen K.H., and Koopman J.S., 2005, The effects of socioeconomic development on worldwide hepatitis A virus seroprevalence patterns, International Journal of Epidemiology, 34(3): 600-609.
https://doi.org/10.1093/ije/dyi062

Kanda T., Nakamoto S., Wu S., Nakamura M., Jiang X., Haga Y., Sasaki R., and Yokosuka O., 2017, Direct-acting antivirals and host-targeting agents against the hepatitis A virus, J Clin Transl Hepatol, 5(2): 119-125.

Khudyakov Y.E., Lopareva E.N., Jue D.L., Fang S., Spelbring J., Krawczynski K., Margolis H.S., and Fields H.A., 1999, Antigenic epitopes of the hepatitis A virus polyprotein, Virology, 260(2): 260-272.
https://doi.org/10.1006/viro.1999.9813

Lemon S.M., Ott J.J., Van Damme P., and Shouval D., 2018, Type A viral hepatitis: A summary and update on the molecular virology, epidemiology, pathogenesis and prevention, J Hepatol., 68(1): 167-184.
https://doi.org/10.1016/j.jhep.2017.08.034

Murhekar M.V., Ashok M., Kanagasabai K., Joshua V., Ravi M., Sabarinathan R., Kirubakaran B.K., Ramachandran V., Shete V., Gupta N., and Mehendale S.M., 2018, Epidemiology of hepatitis A and hepatitis E based on laboratory surveillance data-India, 2014-2017, The American journal of tropical medicine and hygiene, 99(4): 1058.
https://doi.org/10.4269/ajtmh.18-0232

Sayed I.M., 2023, Dual Infection of Hepatitis A Virus and Hepatitis E Virus-What Is Known?, Viruses, 15(2): 298.
https://doi.org/10.3390/v15020298

Schillie S., Vellozzi C., Reingold A., Harris A., Haber P., Ward J.W., and Nelson N.P., 2018, Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, MMWR Recommendations and Reports, 67(1): 1.
https://doi.org/10.15585/mmwr.rr6701a1

Wang X., Ren J., Gao Q., Hu Z., Sun Y., Li X., Rowlands D.J., Yin W., Wang J., Stuart D.I., Rao Z., and Fry E.E., 2015, Hepatitis A Virus and the Origins Of Picornaviruses, Nature, 517(7532): 85-88.
https://doi.org/10.1038/nature13806

Wu M.S., Liu Z.Q., Chen X.D., and Zhang T.J., 2020, Current situation on the global distribution of hepatitis B virus subtypes, Zhonghua Jibing Kongzhi Zazhi (Chinese Journal Of Disease Control & Prevention), 2020, 24(2): 217-221.