جامعة الملك سعود
King Saud University

HEPATITIS A VIRUS

(HAV)

Required for Medical Virology Course

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Introduction

Hepatitis A is an infectious liver disease caused by the hepatitis A virus (HAV).There are other kinds of viral hepatitis such as hepatitis B, hepatitis C, hepatitis D, and hepatitis E. Hepatitis A is the most common form of acute viral hepatitis worldwide. 1991, it was sub classified as a member of the Hepatovirus genus of the family Picornaviridae. The disease varies in clinical severity from a mild illness lasting 1-2 weeks to a severely disabling disease lasting several months. These diseases and the viruses that cause them are not related to hepatitis A although they also affect the liver. They may have other, different symptoms and different modes of transmission. This means that there are different ways of spreading the disease and different means for preventing and controlling these diseases. HAV replicates in hepatocytes and interferes with liver function and causes liver inflammation, the Inflammation is swelling that occurs when tissues of the body become injured or infected, Inflammation can cause organs to not work properly.

History of Disease:

Acute hepatic infects the liver as a result of infection with hepatitis (HAV). Many of the cases have little or no symptoms, especially at a young age. The incubation period (the time between initial contact with the virus and the onset of the disease) for hepatitis A ranges from 15 to 50 days. The length of the incubation period depends on the amount of virus to which a person is exposed. Exposure to a large dose of virus results in a short incubation period. The disease is common in poor Countries. It is an old disease and was described by Hippocrates. Hepatitis A virus is spread by contaminated food and water or from close contact with someone who's infected. The reported incidence of HAV in Canada remained above 4 per 100,000 between 1980 and 1997 and has declined to 1.47 per 100,000 in 2004.

The Distribution of the Disease

1\ Africa

Information on HAV infection in Africa is limited. Available data shows that most of Africa remains a high endemicity region. Almost all black children in South Africa were anti-HAV-positive by the age of 12 years and almost 100% of black adults had antibodies to HAVE before the age of 20 years, while only 30%-40% of white adults were anti-HAV-

positive by the age of 20 years, rising to about 60% by the age of 40-49 years. North Africa has an intermediate level of anti-HAV. Studies from the 1980s showed nearly universal immunity in many countries; a 100% immunity rate by age 10 years was found in Algeria and nearly 100% of adults were anti-HAV positive in Morocco. More recent data shows that, in general, urban areas have experienced a decline in hepatitis A infection, while rates in rural areas remain high and the prevalence is generally lower in higher social classes.

2\ Asia

The spread of HAV virus rates is vary considerably among countries in Asia, with some continuing to have high rates and others moderate or low incidence. Low areas include Japan and others countries such as Taiwan where the prevalence has decreased markedly in the last years. In fact, while in the 1970s the prevalence of anti-HAV in adults was more than 90%, later studies show that in the Taipei area, the prevalence was nearly 0% and in the rural areas only very few adolescents and young adults showed signs of previous infection. In the moderate countries, such as Korea, Indonesia, Thailand, Sri Lanka and Malaysia, the available data shows that the incidence rate may be decreasing, at least in urban areas, and the age at infection increases from very early to late childhood. The number of cases of adult hepatitis A has progressively been increasing

during the last several decades in Korea. In addition, the pattern of age-specific sero prevalence of anti-HAV has changed with economic growth. The prevalence of anti-HAV in the 10-50 year age range has declined rapidly during the last 3 decades. As a result, this age group has a high risk for HAV infection and clinically overt hepatitis A is increasing in adolescents and adults. In China and India, the two most populous countries in the world that have shown a very rapid socio-economic development in the last years, many high endemicity areas for HAV infection coexist with others, making a transition to moderate incidence.

3\ Central and South America

Latin American countries show many of the characteristics of developing countries, with migration from rural communities to cities leading to urban areas of low income and social deprivation. Improvements in public health programs and sanitary conditions have had an impact on the epidemiological patterns of HAV infection in developing economies and so previous studies showing Latin America to be an area of high endemicity with almost universal infection before the age of 10 years may no longer be valid. It is, nevertheless, difficult to estimate the exact incidence of hepatitis. The endemicity patterns continue to be high in several Latin America countries, such as the Central and the Caribbean areas, where studies performed between 1990 and 1999 showed a very high

seroprevalence rate and found that more than half of the children had developed immunity by their second birthday and nearly all adults in both rural and urban areas were immune to HAV. Data from recent studies has shown that the prevalence of anti-HAV is decreasing in several South American countries, including Argentina, Bolivia, Brazil, Venezuela, Chile and Uruguay where there has been a shift from high to medium endemicity. This shift was obtained with the improvements in public health programs and sanitary conditions in most parts of these areas.

Epidemiology

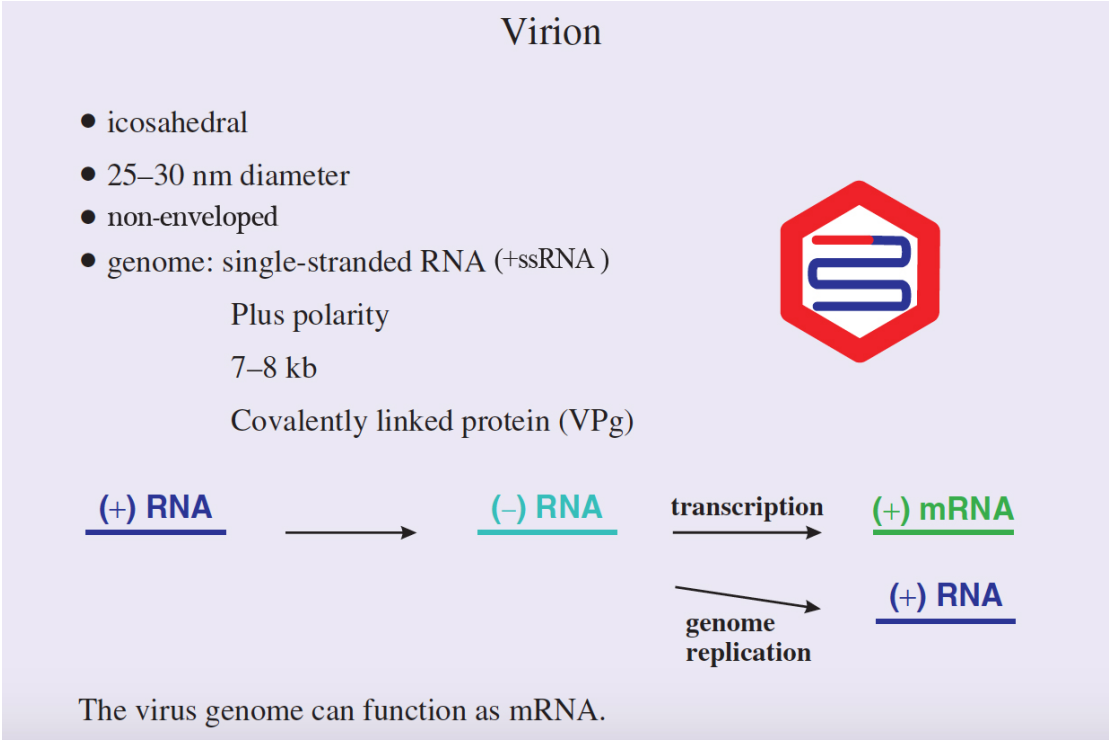
The incidence of HAV infection in the United States has fallen from about 12 cases per 100,000 population in the 1980's to 2.9 in 2002. This is largely due to the availability of the vaccine. In 2001, there were 93,000 new HAV infections in the United States. There were an estimated 45,000 acute clinical cases (but many fewer were actually reported). In the United States hepatitis A outbreaks used to occur in 10 to 15 years cycles since transmission is via the oral members of the family of an infected person are most at risk but in half of all cases no risk factor is identified. Many infected persons are asymptomatic (most children and up to a half of infected adults) but still shed infectious virus. In addition, conditions of poor housing and cramped conditions lead to spread of the virus. The virus is very resistant to a variety of agents including low pH, organic solvents

and detergents. It is also resistant is temperatures as high as 61 degrees for 20 minutes. Besides direct oral transmission (such as by contaminated hands), the virus may be spread in contaminated drinking water and where raw sewage is present since the virus can survive for months in fresh or salt water. The highest rates of hepatitis A in the United States are found in Hispanic and Native American populations. The lowest are among Asian Americans. This undoubtedly reflects socio-economic conditions such as crowding and also contact with persons from countries such as Mexico with high HIV infection rates. These factors result in higher hepatitis A incidence in western state. In 1990, hepatitis A incidence was highest in children (f with about an equal male to female ratio; however, by 2001, the gender/age incidence has changed markedly with the highest incidence in young to middle aged men. This is because the incidence of hepatitis A has fallen as a result of vaccine use and HAVE is now mainly spreading among intravenous drug users and homosexual men. The virus is found worldwide with the highest levels in under-developed countries. In the developed countries all children have anti-HAV antibodies indicative and infection occurs in older individuals and clinical disease is more often seen. Some countries with high health standards clinical disease outbreaks are again rare and hepatitis A is seen primarily in intravenous drug users.

Classification

Order	Picornavirales
Family	picornaviridae
Genus	hepatovirus

Structure and Genome



The genome can be divided into three regions:

5′ non-translated region (5′ NTR), a single open reading frame (ORF), and 3′ non-coding region (3′ NTR).

Genotypes

HAV has seven different genotypes, designated I to VII. Four of these, I, II, III, and VII have been associated with human disease. Genotypes I and III which are further divided into subgenotypes A and B comprise most of the human HAV strains, with 80% of them being genotype I. The other, genotypes IV, V, and VI, each include a single simian HAV strain.

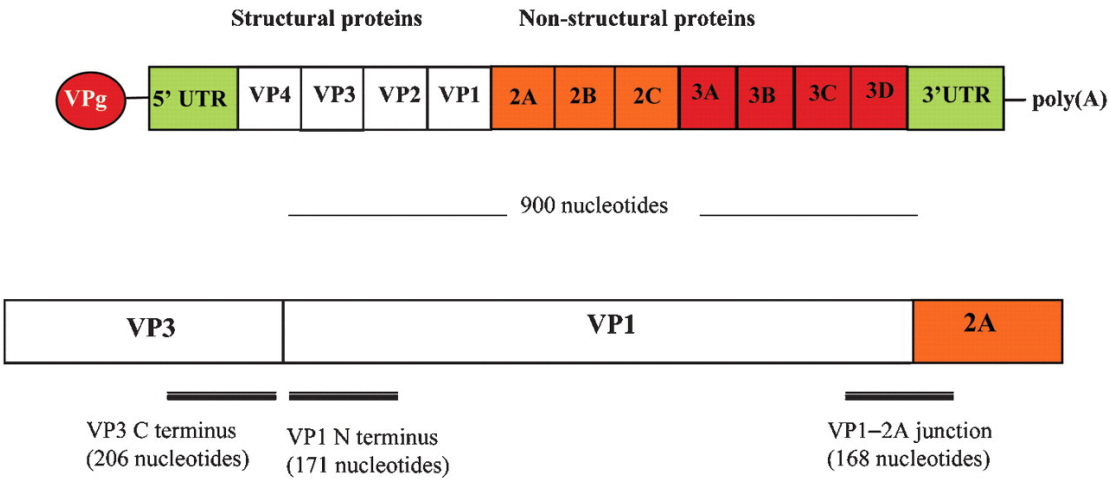
Subgenotype IA is considered as a major cause of acute hepatitis worldwide and has been isolated from all parts of the world.

Proteins:

It can be divided into 3 functional regions, designated P1, P2, and P3. The P1 region encodes capsid polypeptides (VP1, VP2, VP3, and a putative VP4), whereas the P2 and P3 regions encode nonstructural proteins associated with viral replication.

Structural proteins	
Protein	**Function**
VP1 + VP3	The native conformation of the VP1 and VP3 capsid proteins forms a single, dominant, serologic epitope on the viral capsid and elicits a neutralizing antibody response.
VP4	Helping the viral genome cross cell membranes during entry.

Nonstructural functions	
Protein	**Function**
2A	Essential for the formation of pentameric intermediates
2B	Involved in critical process in viral factory formation
2C	Anchor the viral replication complexes to the membranous structure.
3A	Involved in both the rearrangement of the target membranes during infection and the tethering of the RNA replication complex to these membranes.
3B	the primer of viral RNA synthesis
3C	Mediates the primary as well as the secondary cleavages of the HAV polyprotein.
3D	RNA polymerase



Mode of transmission

1-Infection is transmitted by the faecal-oral route from person to person or via fomites.

2- Infectious food handlers may contaminate non-cooked foods such as salads , Food-borne outbreaks are not uncommon and ingestion of shellfish cultivated in polluted water is associated with a high risk of infection.

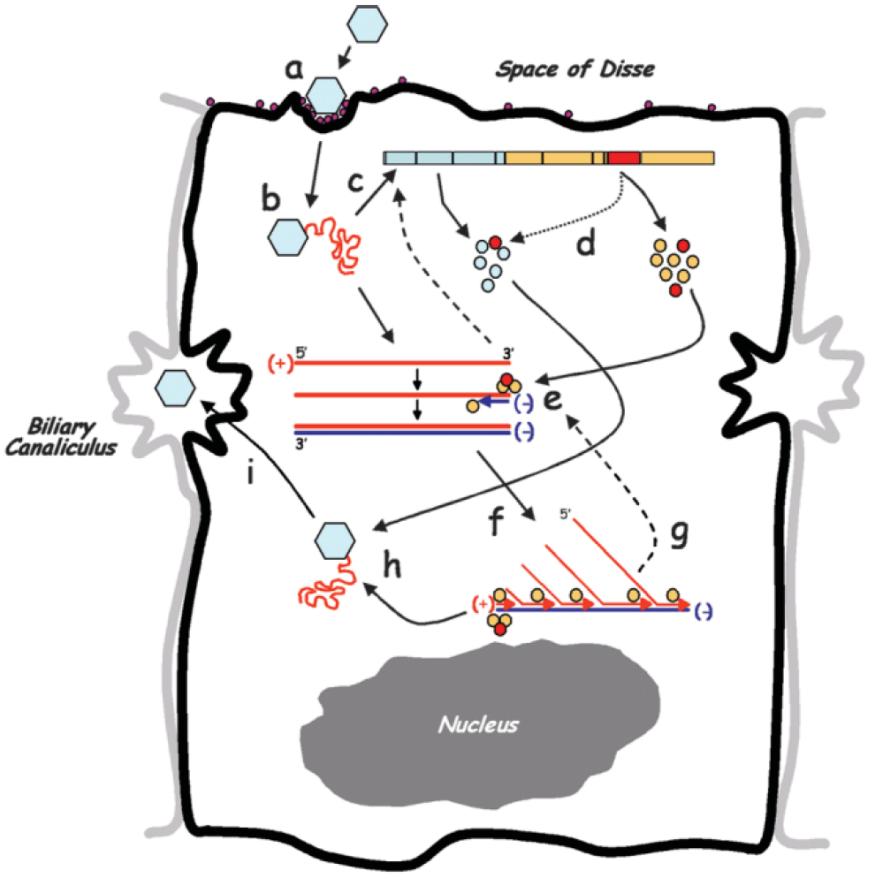
3-The virus spreads by the fecal–oral route, and infections often occur in conditions of poor sanitation and overcrowding.

4- Hepatitis A can be transmitted by the parenteral route, but very rarely by blood and blood products.

5- In developed countries, though, the infection is contracted primarily by susceptible young adults, most of whom are infected with the virus during trips to countries with a high incidence of the disease or through contact with infectious persons.

6- In developing countries, and in regions with poor hygiene standards, the rates of infection with this virus are high and the illness is usually contracted in early childhood. As incomes rise and access to clean water increases, the incidence of HAV decreases.

Replication Cycle:



(a) The virus enters the hepatocyte via an interaction with a cellular receptor, the identity of which remains uncertain.

(b) This is followed by uncoating of the viral particle and release of the positive-sense RNA genome into the cell.

(c) An internal ribosome entry site within the 5 nontranslated segment of the genome mediates cap-independent translation of the viral polyprotein.

(d) The polyprotein undergoes co- and post-translational proteolytic processing directed by the viral protease, $3C^{pro}$.

(e) Non- structural viral proteins assemble into a membrane-bound RNA replicase, bind the 3 end of the genomic RNA and commence synthesis of a negative-strand copy of the viral genome.

(f) The negative-strand copy of the genome is used as template for synthesis of multiple new copies of genomic positive-strand RNA.

(g) Some of this newly synthesized positive-sense RNA is recycled for further RNA synthesis or translation (dashed lines).

(h) Other positive-strand RNA molecules are packaged into new viral particles formed by assembly of the structural proteins, followed by final cleavage of the VP1-2A precursor by an unknown cellular protease (VP1/2A junction), and the "maturation" cleavage of the VP4/VP2 junction.

(i) Newly assembled HAV particles are secreted by the cell across the apical membrane of the hepatocyte into the biliary canaliculus, from which they are passed into the bile and small intestine.

Genus	**Host details**	**Tissue tropism**	**Entry details**	**Release details**	**Replication site**	**Assembly site**	**Transmission**
Hepatovirus	Humans; vertebrates	Liver	Cell receptor endocytosis	Lysis	Cytoplasm	Cytoplasm	Oral-fecal; blood

Symptoms:

The patient can get the first symptoms anytime between 15 and 50 days after he/she came in contact with the virus but they usually show up between about 2 and 4 weeks later.

Most people with hepatitis A usually have:

- Extreme tiredness
- Loss of appetite
- Muscle aches and pains
- Nausea and vomiting
- Low-grade fever

Several days later, some symptoms of liver problems can show up. The patient may have:

- Dark urine
- Light-colored bowel movements
- Yellow skin (jaundice). It's less common in children under age 6.
- Yellowing of the white part of your eyes
- Stomach pain
- Itchy skin

If a child has Hep A, he may also have:

- Cold symptoms
- Cough
- Sore throat

If the person over age 50 or have a long-term liver disease, He/She may has a more severe case of the disease called fulminant hepatitis A infection. the symptoms could be like:

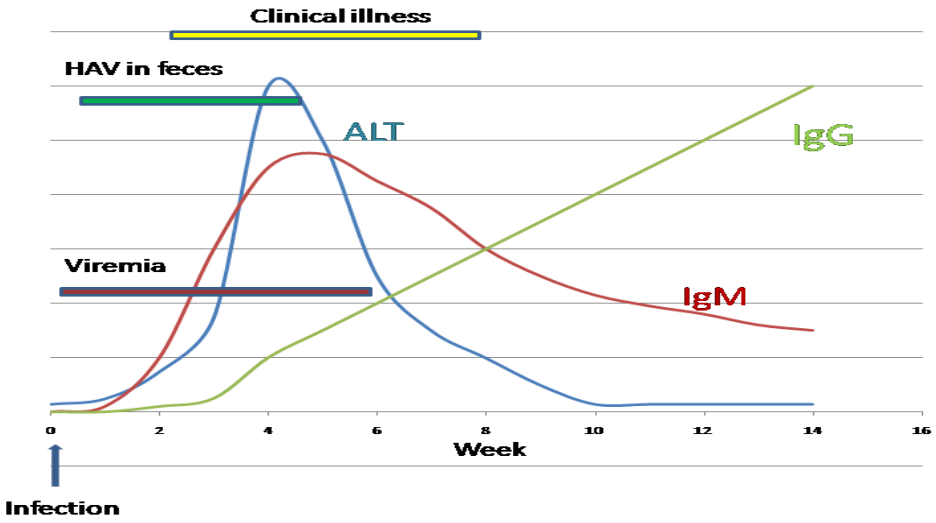
- Blood clotting problems
- Confusion and changes in alertness
- Liver function continues to get worse
- Yellowing of the skin and eyes that gets worse

The doctor may spot some more signs for the disease

- Swollen liver and spleen
- Tenderness in the right upper side of your belly

Diagnosis

1- ELISA



Although HAV is excreted in the feces towards the end of the incubation period, specific diagnosis is made by the detection of HAV-specific IgM antibodies in the blood. IgM antibody is only present in the blood following an acute hepatitis A infection. It is detectable from one to two weeks after the initial infection and persists for up to 14 weeks. The presence of IgG antibodies in the blood means the acute stage of the illness is past and the person is immune to further infection. IgG antibodies to HAV are also found in the blood following vaccination, and tests for immunity to the virus are based on the detection of this antibody. During the acute phase , liver dysfunction is indicated by raised serum bilirubin and transaminase and a depressed prothrombin level . The specific diagnosis is readily made by an **ELISA** test for specific IgM .During the early stage of jaundice the virus can be identified in the faeces by IEM .

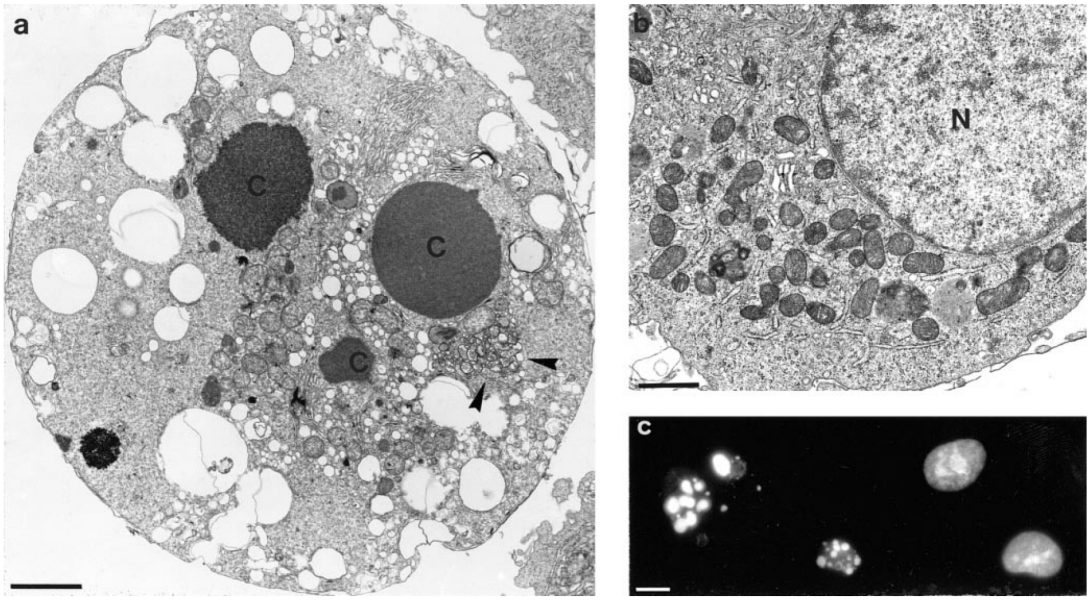
2- Nucleic Acid Sequencing

Nucleic acid sequencing is performed on PCR products to confirm their specificity and provide the ultimate means to identify and characterize the organism. Nucleic acid sequencing of selected genomic regions of HAV has been used to determine the genetic relatedness of isolates. The original nucleic acid sequencing methodology described by Sanger et al. which required independent labeling reactions for each nucleotide and conventional gel electrophoresis, has been replaced by high-throughput methods, including fluorescent dyes for label terminators and capillary arrays for electrophoresis, which have improved sequencing speed and accuracy.

Genome detection by RT PCR is a rapid and sensitive method.

Cytopathic Effect

Unlike the other members of the family, HAV requires a long adaptation period to grow in cell culture, replicates slowly and rarely produces a cytopathic effect.



Experiments performed with the HM175/24a indicated that FRhK-4 cells were infected. Ultrastructural analysis show 3 modifications:

a- Nuclear membrane was destroyed

b- Chromatin was fragmented and appeared as compact areas in the cytoplasm

c- The cell contains a HAV-induced tubular±vesicular network (arrowheads) near Endoplasmic reticulum.

Prevention and Control of Virus

The hepatitis A vaccine offers immunity to adults and children older than age 1. The Centers for Disease Control and Prevention recommends routine hepatitis A vaccination for children aged 12 to 23 months and for adults who are at high risk for infection. Treatment with immune globulin can provide short-term immunity to hepatitis A when given before exposure or within 2 weeks of exposure to the virus.

Within households, good personal hygiene, including frequent and proper hand washing after bowel movement and before food preparation, are important measures to reduce the risk of transmission from infected individuals before and after their clinical disease becomes apparent.

Treatment of Hepatitis A

There is no specific treatment for hepatitis A virus infection. Treatment and management of HAV infection are supportive. prevention is the most effective approach against the disease.

hepatitis A vaccine was primarily targeted to persons at increased risk for HAV infection, particularly international travelers. While this strategy prevented infection in this group and in other vaccinated individuals, it had little or no impact on the incidence of HAV infection.

Table 1. Vaccines to prevent hepatitis A

VACCINE	TRADE NAME (MANUFACTURER)	AGE (Y)	DOSE	ROUTE	SCHEDULE	BOOSTER
Hepatitis A vaccine, inactivated	Havrix (GlaxoSmithKline)	1–18 ≥19	0.5 mL (720 ELU) 1.0 mL (1,440 ELU)	IM IM	0, 6–12 mo 0, 6–12 mo	None None
Hepatitis A vaccine, inactivated	Vaqta (Merck & Co., Inc.)	1–18 ≥19	0.5 mL (25 U) 1.0 mL (50 U)	IM IM	0, 6–18 mo 0, 6–18 mo	None None
Combined hepatitis A and B vaccine	Twinrix (GlaxoSmithKline)	≥18 (primary) ≥18 (accelerated)	1.0 mL (720 ELU HAV + 20 µg HBsAg) same as above	IM IM	0, 1, 6 mo 0, 7, 21–30 d	None 12 mo

Host Immune Defense

Hepatitis A virus (HAV) is transmitted by the fecal-oral route. The virus crosses through the gastrointestinal tract by an uncharacterized mechanism and travels to the liver, where it replicates in hepatocytes. It is released into the bloodstream and is simultaneously present in the bile and shed in the feces. Fecal shedding and viremia are maximal at the onset of liver function abnormalities and terminate about the time humoral immunity is detected, approximately 28 days after exposure. IgM, IgA, and IgG anti-HAV antibodies are usually present at onset of symptoms.

Although the IgM response becomes undetectable usually within 6 months, IgG responses frequently persist for life, providing protection against reinfection. Pre- and postexposure immunization with pooled human serum immunoglobulin (ISG) is approximately 90% effective in preventing hepatitis A. Recipients of ISG have very low levels of detectable anti-HAV antibodies, and vaccines that elicit anti-HAV levels comparable with those produced by ISG should confer similar protection.

Mutations in both the 2B and 2C genes of hepatitis A virus are involved in adaptation to growth in cell culture.

Oligonucleotide-directed mutagenesis of an infectious cDNA clone of wild-type hepatitis A virus was performed to determine which mutations acquired in the nonstructural 2B and 2C genes during adaptation to growth in cell culture were effective in enhancing virus growth in vitro. Results of transfection assays demonstrated that one mutation in the 2B gene and two mutations in the 2C gene were responsible for an increased efficiency in growth, but growth enhancement required the participation of at least two of the three mutations.

Recent discoveries

This virus is old virus and is not have new discoveries about it

References

- Adrian L, Garriga D, Buxaderas M, Fraga J, Pereira P, Ribeiro, S Veraguer N (2015) *Structural Basis for Host Membrane Remodeling Induced by Protein 2B of Hepatitis A Virus.*
- Carter J, Saunders V (2007) *Virology; Priciples and Applications.*
- Ciervo A, Beneduce F, Morace G (1998) *Polypeptide 3AB of Hepatitis A Virus Is a Transmembrane Protein.*
- Hussain Z (2011*) Hepatitis A: Clinical, Epidemiological and Molecular Characteristics.*
- Martin A, Lemon S (2006) *Hepatitis A: From Discovery to Vaccines*.
- Nainan O, Xia G, Vaughan C, Margolis H, (2006) *Diagnosis of Hepatitis A Virus Infection: a Molecular Approach.*
- National Digestive Diseases Information Clearinghouse (2008) *Viral Hepatitis: A through E and Beyond.*
- Shukla A, Padhi A, Gomes J, Banerjee M (2014) *The VP4 peptide of hepatitis A virus ruptures membranes through formation of discrete pores.*
- Stapleton J (1995) *Host immune response to hepatitis A virus.*
- Thanh H (2010) *Detection of hepatitis A virus in bivalve molluscs in Southern Vietnam using RT-PCR.*
- Goser R, Egger D, Bienz K (2000) *Topathic and a Cell Culture Adapted Hepatitis A Virus Strain Differ in Cell Killing but Not in Intracellular Membrane Rearrangements*
- Wiley J, Ltd S (2004) *Principle and Practice of Clinical Virology.*
- http://www.webmd.com/hepatitis/hepa-guide/hepatitis-a-symptoms
- https://en.wikipedia.org/wiki/Picornavirus