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Hepatitis A

World Health Organization
Department of Communicable Disease Surveillance and Response

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Hepatitis A - an introduction

Hepatitis is a general term meaning inflammation of the liver and can be caused by a variety of different viruses such as hepatitis A, B, C, D and E. Since the development of jaundice is a characteristic feature of liver disease, a correct diagnosis can only be made by testing patients' sera for the presence of specific anti-viral antibodies.[22, 40]

Hepatitis A, one of the oldest diseases known to humankind, is a self-limited disease which results in fulminant hepatitis and death in only a small proportion of patients. However, it is a significant cause of morbidity and socio-economic losses in many parts of the world.[18, 40]

Transmission of HAV is typically by the faecal-oral route.[18, 23, 39, 40]

Infections occur early in life in areas where sanitation is poor and living conditions are crowded. With improved sanitation and hygiene, infections are delayed and consequently the number of persons susceptible to the disease increases. Under these conditions explosive epidemics can arise from faecal contamination of a single source.

Hepatitis A was formerly called Infectious hepatitis, Epidemic hepatitis, Epidemic jaundice, Catarrhal jaundice, Type A hepatitis, HA.[18, 40]

What causes the disease?

Hepatitis A is caused by infection with the hepatitis A virus (HAV), a nonenveloped, positive stranded RNA virus, first identified by electron microscopy in 1973, classified within the genus hepatovirus of the picornavirus family.[18, 23]

The virus interferes with the liver's functions while replicating in hepatocytes. The individual's immune system is then activated to produce a specific reaction to combat and possibly eradicate the infectious agent. As a consequence of pathological damage, the liver becomes inflamed.

How is HAV spread?

HAV is transmitted from person-to-person via the faecal-oral route.[18, 23]

As HAV is abundantly excreted in faeces, and can survive in the environment for prolonged periods of time, it is typically acquired by ingestion of faeces-contaminated food or water. Direct person-to-person spread is common under poor hygienic conditions.[22]

Occasionally, HAV is also acquired through sexual contact (anal-oral) and blood transfusions.[22]

Who is susceptible to infection?

People who have never contracted HAV and who are not vaccinated against hepatitis A, are at risk of infection.

The risk factors for HAV infection are related to resistance of HAV to the environment, poor sanitation in large areas of the world, and abundant HAV shedding in faeces.[18]

In areas where HAV is highly endemic, most HAV infections occur during early childhood.

Where is HAV a problem?

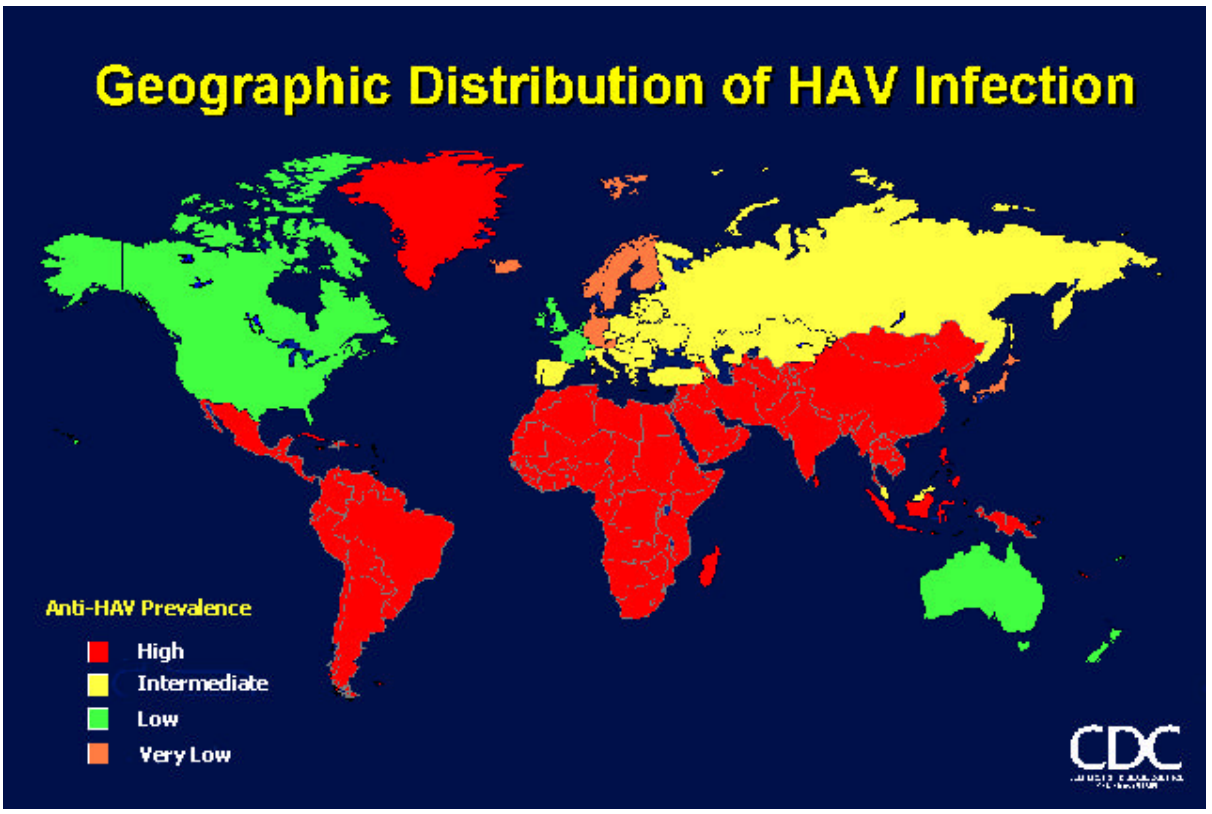
The virus is present worldwide, and the risk of infection is inversely proportional to levels of sanitation and personal hygiene.[23]

In developing countries with poor environmental hygienic conditions, nearly all children are infected with HAV before the age of 9. There is substantial underestimation of hepatitis A cases in these areas, because HAV infections for young children are mostly asymptomatic and therefore unrecognized.

As sanitation conditions improve, transmission shifts to older age groups and the incidence of symptomatic disease increases.

In most developed countries, endemic HAV transmission is unlikely.

World distribution map



From: Centers for Disease Control and Prevention (CDC), Atlanta, USA:[10]
http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep16.gif

Endemicity patterns (low, intermediate and high) of hepatitis A virus infection worldwide. (Note: this map generalizes available data and patterns may vary within countries).[9, 10]

When is hepatitis A contagious?

In persons who develop clinically apparent hepatitis A, secretion of virus in stool at high titres begins one to three weeks prior to onset of illness, and may continue for several weeks at lower titres after jaundice occurs.[21]

Although the level of virus shedding does not correlate with the severity of liver disease, faeces are highly infectious and therefore extremely contagious during all of this period.

Why is there no treatment for the acute disease?

Hepatitis A is a viral disease, and as such, antibiotics are of no value in the treatment of the infection.

Antiviral agents, as well as corticosteroids, have no effect in the management of the acute disease.[18]

The administration of immune globulins (IG) may help preventing or improving the clinical manifestations of the disease if given within 2 weeks of infection, but it is of no help in the acute phase of hepatitis A.[18, 39]

Therapy can only be supportive and aimed at maintaining comfort and adequate nutritional balance.[18]

Complete recovery without therapy is generally the rule.[18]

The hepatitis A virus HAV

HAV, first identified in 1973, is a nonenveloped, spherical, positive stranded RNA virus, classified within the genus hepatovirus of the picornavirus family.[18, 21-23]

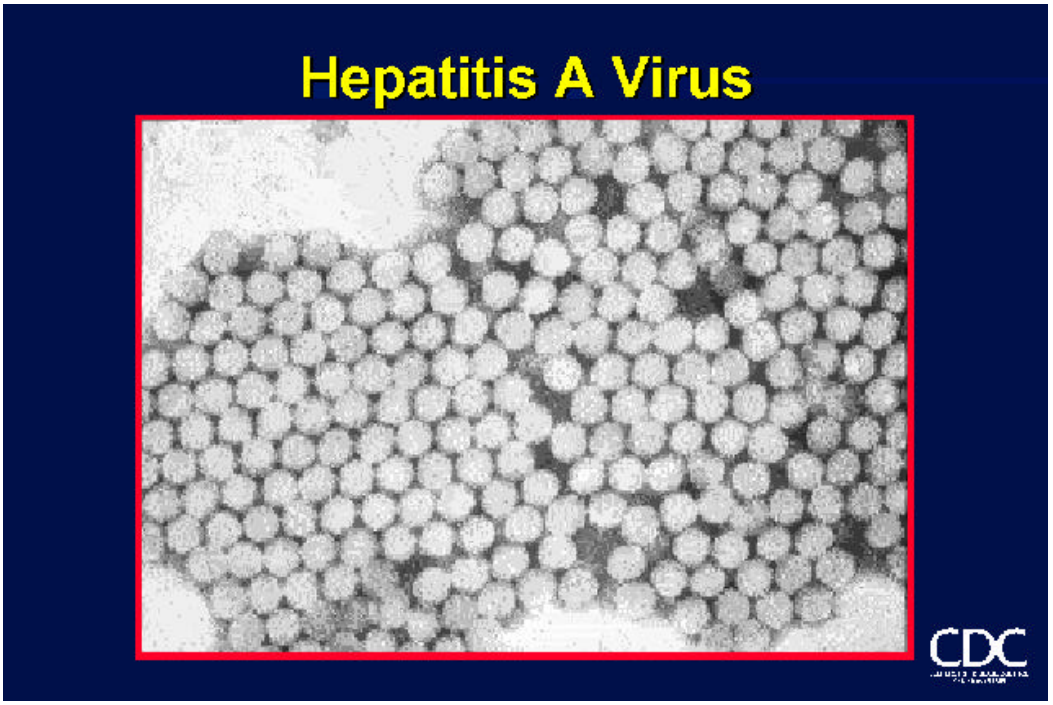
HAV infection does not lead to chronic or persistent hepatitis.[18, 23, 40]

HAV strains recovered from widely separated regions of the world are antigenically similar. In humans, a single serotype of HAV exists.[18, 21, 23, 39, 40]

HAV is known to produce disease in humans and non-human primates. In vitro, the wild type virus is generally difficult to grow and no cytopathic effect is observed. Attenuated HAV strains adapted to cell culture have been used to develop vaccines.[18, 21, 23, 40]

HAV infection induces lifelong protection against reinfection.[18]

Electron Microscopy (EM) picture



From: Centers for Disease Control and Prevention (CDC), Atlanta, USA:[10]
http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep06.gif
Electron microscopy picture of human hepatitis A virus.

Morphology and physicochemical properties

HAV is among the smallest and structurally simplest of the RNA animal viruses.

The virion is nonenveloped and, with a diameter of 27-32 nm, it is composed entirely of viral protein and RNA. Electron microscopy (EM) analyses show particles with icosahedral symmetry although no structural details could be discerned. Morphologically, HAV particles are indistinguishable from other picornaviruses.[18, 22, 40]

Full virions have a buoyant density of 1.32 - 1.34 g/cm^3 in CsCl and a sedimentation coefficient of 156 - 160 S in neutral sucrose solutions.[18, 21]

Empty capsids, abundant in faeces collected during early infection, band at 1.20 and 1.29 - 1.31 g/cm^3, with sedimentation coefficients ranging from 50 S to 90 S, predominantly 70 S.[18, 21]

Genome and proteins

The hepatitis A genome consists of a linear, single stranded, positive-sense RNA of approximately 7.5 kb containing a 5'-nontranslated region with complex secondary and tertiary structure.[18, 21, 22, 40]

The 5'-end represents a noncoding region (NCR) extending over 10% of the genome, it is uncapped and covalently linked to the viral protein VPg (2.5 kD).[18, 21, 22, 40]

A single large polyprotein is expressed from a large open reading frame extending through most of the genomic RNA. This polyprotein is subsequently cleaved by a viral protease (3C^{pro}) to form three (possibly four) capsid proteins and several nonstructural proteins.[18, 21-23, 40]

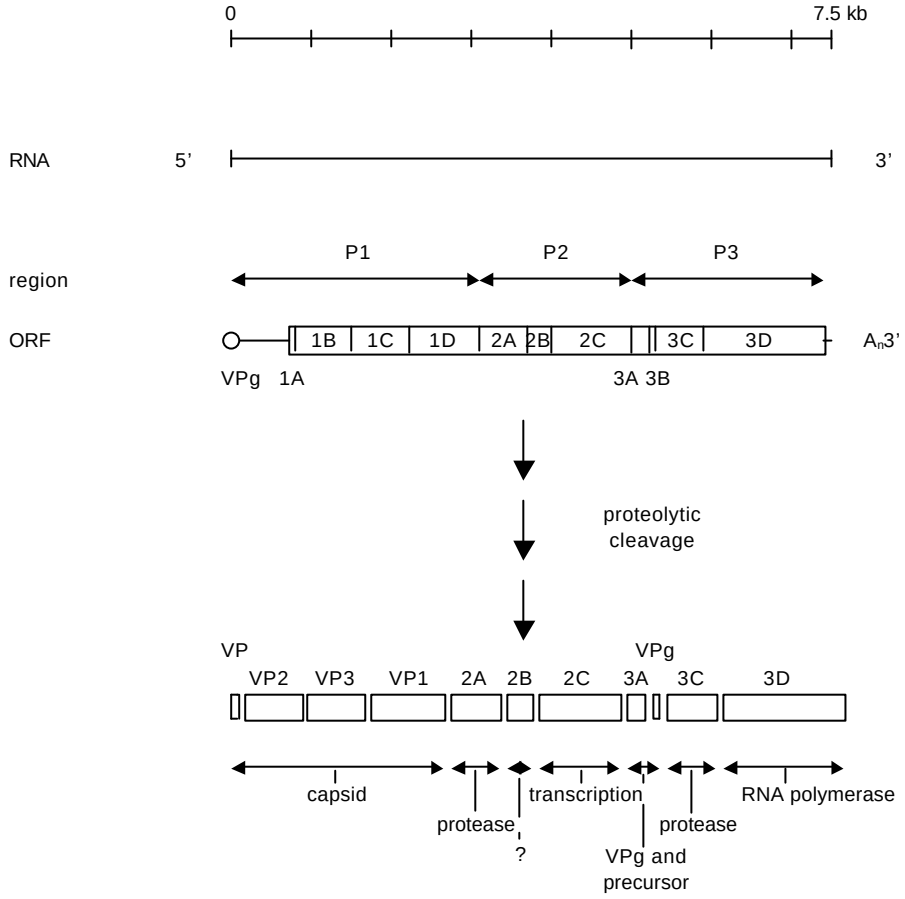
The 3'-end terminates with a poly(A)tail of 40 - 80 nucleotides.[18, 22]

Hepatitis A capsids contain 60 copies of VP1 (30 to 33 kD), VP2 (24 to 30 kD) and VP3 (21 to 28 kD). Exposed parts of VP1 (residues Ser102 and Ser114) and of VP3 (residue Asp70) on the capsid surface define the conformational immunodominant antigenic site of HAV.[18, 22, 23, 40]

Sequences for known human HAV isolates are highly similar even when geographic and temporal origins are widely separated, yet seven distinct genotypes have been identified to date.[18]

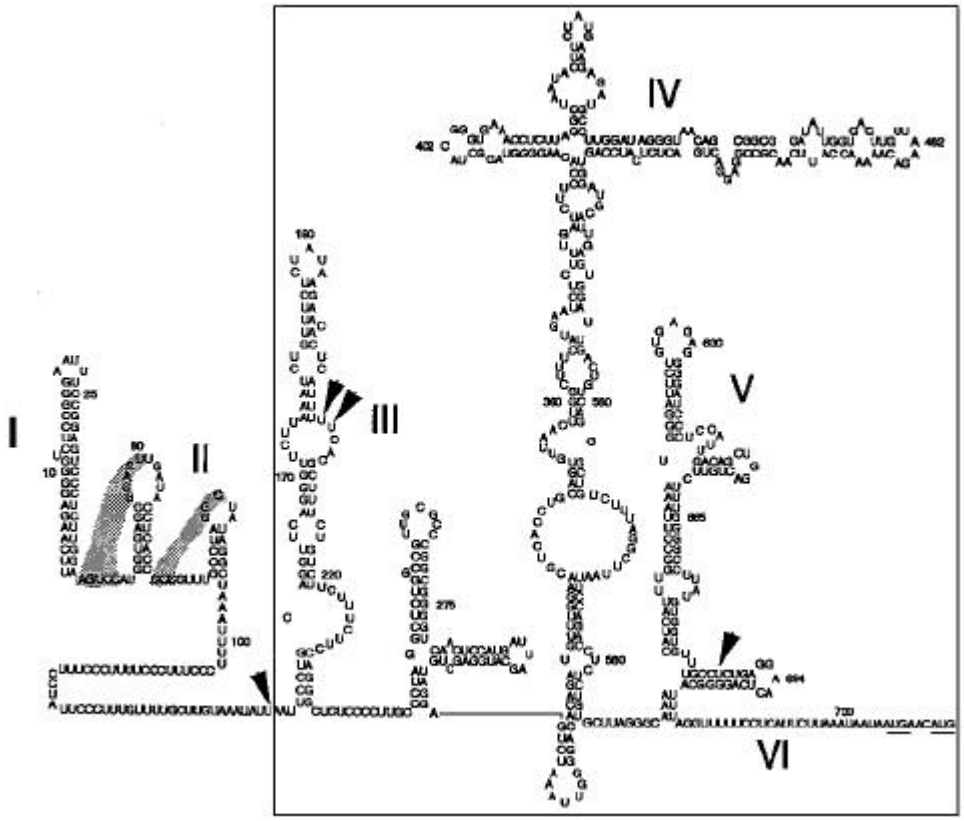
HAV genomic replication occurs exclusively in the cytoplasm of the infected hepatocyte by a mechanism involving an RNA-dependent RNA polymerase.[21]

Genetic structure of hepatitis A virus



Delineation, to scale, of the genome of HAV with its 5'-linked VPg protein, 5'-nontranslated region, single long open reading frame, 3'-nontranslated region and polyadenylated 3'-end. The RNA is translated into a precursor polyprotein that is cleaved to generate mature proteins.[6]

Proposed secondary structure of the 5' NCR of HAV RNA



From: Lemon SM and Robertson BH. Current perspectives in the virology and the molecular biology of hepatitis A virus. Seminars in Virology, 1993, 4:285-295,[25] with permission.

Proposed secondary structure of the 5’ NCR of HAV RNA (strain HM175/wild-type). This model is based on a combination of phylogenetic comparisons, thermodynamic predictions, and nuclease digestions of synthetic RNA between nucleotides 300 and 735. Major structural domains are indicated by Roman numerals beginning at the 5’ terminus. Domains contributing to the HAV internal ribosome entry site are included in the box, although the boundaries are not precisely determined. Sites of mutations that appear to enhance HAV replication in cell culture are indicated (arrows). Two possible pseudoknots are indicated by shaded interactions near the 5’ terminus. The two initiation codons for the open reading frame (nucleotides 735 to 737 and 741 to 743) are underlined.[25]

Antigenicity

HAV has only one known serotype, and one neutralization site is immunodominant. Different viral strains show similar reactivity to monoclonal anti-HAV antibodies.[18, 22, 39, 40]

Antigens of the intact virion are conformational and different from those of isolated proteins. Antibodies to purified capsid proteins or to synthetic peptides have weak or no detectable neutralizing activity.[18, 23]

HAV is neutralized by both anti-HAV IgG and anti-HAV IgM.

No serologic or hybridizing cross-reactivity between HAV and other viral hepatitis agents, including hepatitis E virus (HEV), have been observed.[18, 22]

The nonstructural proteins of HAV are also immunogenic during natural and experimental infections.[18]

Stability

HAV has no lipid envelope and is stable when excreted from the infected liver to the bile to enter the gastrointestinal tract. It has been found to survive in experimentally contaminated fresh water, seawater, wastewater, soils, marine sediment, live oysters, and creme-filled cookies.

HAV is extremely resistant to degradation by environmental conditions, a property that allows its maintenance and spread within populations.[18, 22, 39, 40]

HAV is resistant to:
- thermal denaturation (survives at 70°C for up to 10 min)
- acid treatment (pH 1 for 2 h at room temperature), 20% ether, chloroform, dichlorodifluoromethane, and trichlorotrifluoroethane
- perchloracetic acid (300 mg/l for 15 min at 20°C)
- detergent inactivation (survives at 37°C for 30 min in 1% SDS)
- storage at –20°C for years

HAV is inactivated by:
- heating to 85°C for 1 min
- autoclaving (121°C for 20 min)
- ultraviolet radiation (1.1 W at a depth of 0.9 cm for 1 min)
- formalin (8% for 1 min at 25°C)
- â-propriolactone (0.03% for 72 h at 4°C)
- potassium permanganate (30 mg/l for 5 min)
- iodine (3 mg/l for 5 min)
- chlorine (free residual chlorine concentration of 2.0 to 2.5 mg/l for 15 min)
- chlorine-containing compounds (3 to 10 mg/l sodium hypochlorite at 20°C for 5 to 15 min)
- shellfish from contaminated areas should be heated to 90°C for 4 min or steamed for 90 sec

The disease

The course of hepatitis A may be extremely variable.[18]

Patients with inapparent or subclinical hepatitis have neither symptoms nor jaundice. Children generally belong to this group. These asymptomatic cases can only be recognized by detecting biochemical or serologic alterations in the blood.[18, 22, 40]

Patients may develop anicteric or icteric hepatitis and have symptoms ranging from mild and transient to severe and prolonged, from which they recover completely or develop fulminant hepatitis and die (see below). The severity of the disease increases with age at time of infection.[18, 23]

The course of acute hepatitis A can be divided into four clinical phases:[18, 21-23, 40]

- an incubation or preclinical period, ranging from 10 to 50 days, during which the patient remains asymptomatic despite active replication of the virus. In this phase, transmissibility is of greatest concern.

- a prodromal or preicteric phase ranging from several days to more than a week, characterised by the appearance of symptoms like loss of appetite, fatigue, abdominal pain, nausea and vomiting, fever, diarrhoea, dark urine and pale stools, followed by

- an icteric phase, during which jaundice develops at total bilirubin levels exceeding 20 - 40 mg/l. Patients often seek medical help at this stage of their illness. The icteric phase generally begins within 10 days of the initial symptoms. Fever usually improves after the first few days of jaundice. Viremia terminates shortly after hepatitis develops, although faeces remain infectious for another 1 - 2 weeks. Extrahepatic manifestations of hepatitis A are unusual. Physical examination of the patient by percussion can help to determine the size of the liver and possibly reveal massive necrosis. The mortality rate is low (0.2% of icteric cases) and the disease ultimately resolves. Occasionally, extensive necrosis of the liver occurs during the first 6 - 8 weeks of illness. In this case, high fever, marked abdominal pain, vomiting, jaundice and the development of hepatic encephalopathy associated with coma and seizures, are the signs of fulminant hepatitis, leading to death in 70 - 90% of the patients. In these cases mortality is highly correlated with increasing age, and survival is uncommon over 50 years of age. Among patients with chronic hepatitis B or C or underlying liver disease, who are superinfected with HAV, the mortality rate increases considerably.

- a convalescent period, where resolution of the disease is slow, but patient recovery uneventful and complete. Relapsing hepatitis occurs in 3 - 20% of patients 4 to 15 weeks after the initial symptoms have resolved. Cholestatic hepatitis with high bilirubin levels persisting for months is also occasionally observed. Chronic sequelae with persistence of HAV infection for more than 12 months are not observed.

Predicted outcome of HAV infection

	PREDICTED OUTCOME	
parameter	**Children (<5 years)**	**adults**
Inapparent infection	80-95%	10-25%
Anicteric or icteric disease	5-20%	75-90%
Complete recovery	99+%	98+%
Chronic disease	none	
Mortality rate: #14 years	0.1%	
15-39 years	0.3%	
$40 years	2.1%	

From Hollinger FB and Ticehurst JR. Hepatitis A virus. In: Fields Virology, 3rd ed. Philadelphia, Lippincott - Raven, 1996:735-782,[18] with permission (http://lww.com).

Diagnosis

Since both clinically and biochemically, acute hepatitis due to HAV cannot be distinguished from that due to the other hepatitis viruses, serologic tests are necessary for a virus-specific diagnosis.[18, 21]

Diagnosis of hepatitis is made by biochemical assessment of liver function (laboratory evaluation of: urine bilirubin and urobilinogen, total and direct serum bilirubin, ALT and/or AST, alkaline phosphatase, prothrombin time, total protein, serum albumin, IgG, IgA, IgM, complete blood count).[18, 21-23, 40]

The specific routine diagnosis of acute hepatitis A is made by finding anti-HAV IgM in the serum of patients. A second option is the detection of virus and/or antigen in the faeces.[21, 23]

Virus and antibody can be detected by commercially available RIA, EIA or ELISA kits. These commercially available assays for anti-HAV IgM and total anti-HAV (IgM and IgG) for assessment of immunity to HAV are not influenced by the passive administration of IG, because the prophylactic doses are below detection level.[23]

At the onset of disease, the presence of IgG anti-HAV is always accompanied by the presence of IgM anti-HAV. As IgG anti-HAV persists lifelong after acute infection, detection of IgG anti-HAV alone indicates past infection.[18, 21, 40]

Virus may still be present in the absence of detectable HAV antigen, as demonstrated by the use of more sensitive methods.[18]

If laboratory tests are not available, epidemiologic evidence can help in establishing a diagnosis.

Host immune response

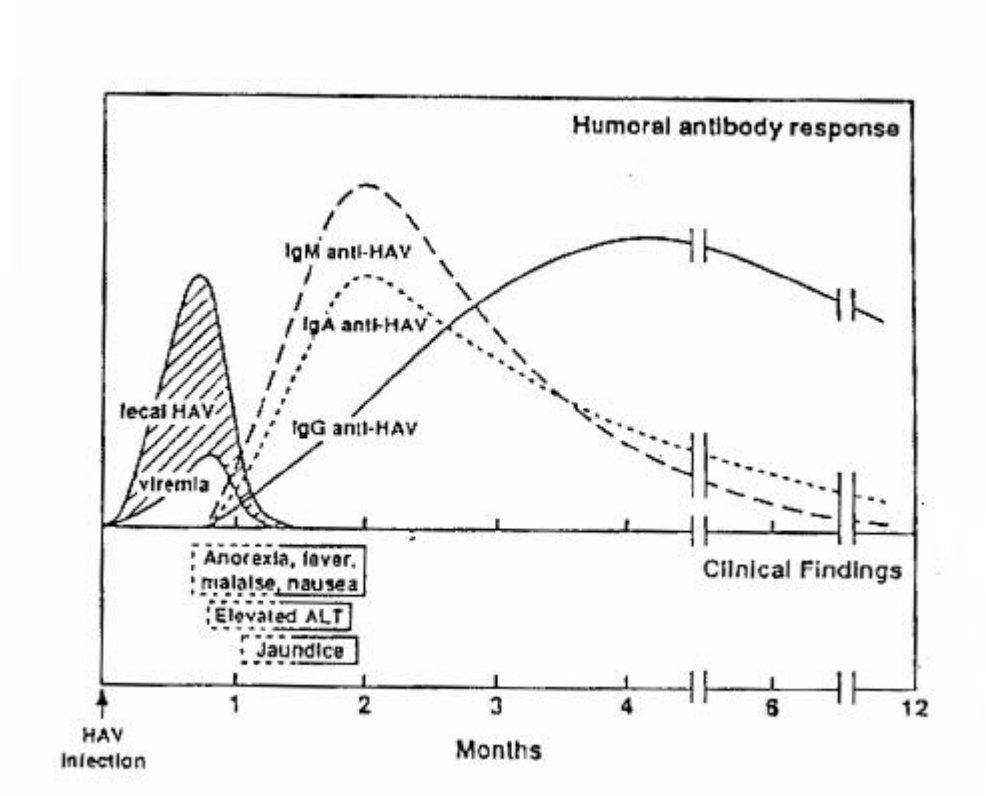
In acute hepatitis A, the presence of anti-HAV IgM is detectable about 3 weeks after exposure, its titre increases over 4 to 6 weeks, then declines to nondetectable levels generally within 6 months of infection.[18, 21-23, 40]

Anti-HAV IgA and IgG are detectable within a few days of the onset of symptoms. IgG antibodies persist for years after infection and provide lifelong immunity.[18, 21-23, 39, 40]

The development of antibody to HAV coincides with a decrease in quantity of viremia and faecal shedding of virus.

Saliva and faeces generally do not contain neutralizing antibodies.[22, 40]

Typical serologic course



From: Stapleton JT and Lemon SM. Hepatitis A and hepatitis E. In: Hoeprich PD, Jordan MC, and Ronald AR, eds. Infectious Diseases, 5th ed. Philadelphia, Lippincott Co, 1994:790-797,[40] with permission (http://lww.com).

Summary of clinical, virologic, and serologic findings in uncomplicated acute hepatitis A.

Prevalence

The highest prevalence of faecal-oral infection occurs in regions where low standards of sanitation promote the transmission of the virus.[22]
In most industrialized nations, where hepatitis A is no longer considered a childhood disease, infections with HAV are increasingly contracted by adults.[31, 40]

Despite the high prevalence of antibody in highly endemic populations, the virus perpetuates in the region due to its high physical stability.

Pathogenesis

Virus-induced cytopathology may not be responsible for the pathologic changes seen in HAV infection as liver disease may result primarily from immune mechanisms. Antigen-specific T-lymphocytes are responsible for the destruction of infected hepatocytes.[18, 21-23, 39]

Increased levels of interferon have been detected in the serum of HAV-infected patients and are presumably responsible for the reduction in virus burden seen in patients following the onset of clinical disease and in their symptoms.[18]

Rarely, patients with acute viral hepatitis A develop features of cholestasis.[18]

Confluent hepatic necrosis may lead to fulminant hepatitis and death in 30 -60% of cases. Death appears to be inevitable when necrosis involves more than 65 - 80% of the total hepatocyte fraction. In patients who survive an episode of acute fulminant hepatic failure, neither functional nor pathologic sequelae are common, despite the widespread necrosis.[18]

During the recovery stage, cell regeneration is prominent. The damaged hepatic tissue is usually restored within 8 to 12 weeks.[18]

Transmission

HAV is generally acquired by the faecal-oral route by either person-to-person contact or ingestion of contaminated food or water. Hepatitis A is an enteric infection spread by contaminated excreta.[9, 18, 23, 40]

High concentrations of virus are shed in the stools of patients during 3 to 10 days prior to the onset of illness till one - two weeks after the onset of jaundice. Faecal excretion of HAV persists longer in children and in immunocompromised persons (up to 4 - 5 months after infection) than in otherwise healthy adults. Communicability is highest during this interval.[18]

Hepatitis A may be acquired from faecally contaminated food or water and from wastewater-contaminated drills or water supplies.[18, 22]

HAV present in sewage-contaminated fresh or salt water can be concentrated by mollusc-like oysters and

clams, which can be an important source of infection if eaten raw or inadequately cooked. Cooked food may become recontaminated after cooking during inappropriate handling.[18]

Transmission by blood transfusion is rare: the donor must be in the viremic prodromal phase of infection at the time of blood donation. Current blood practices do not include screening of donors for evidence of active HAV infection.[18, 22, 23, 40]

Substantial viremia persisting for several weeks suggests the possible role of needle-borne transmission of virus among intravenous drug users, although HAV concentrations in blood are manifold lower than in faeces.

Outbreaks (1992) have occurred among haemophiliacs receiving factor VIII concentrates prepared by a solvent-detergent inactivation process which did not reduce the infectivity of nonenveloped viruses.[18, 23, 38]

HAV is not transmitted from infected mothers to newborn infants, as anti-HAV IgG antibodies present during initial stages of HAV infection cross the placenta and provide protection to the infant after delivery.

Transmission by exposure to urine, nasopharyngeal secretions or aerosol of infected persons is improbable, regardless of the stage of infection. Transmission of HAV by biting insects is conceivable.[18]

Role of non-human primates in the transmission of HAV

Various monkey species such as chimpanzees, owl monkeys, cynomolgus monkeys, rhesus monkeys, stump-tailed monkeys, African green monkeys, tamarins, marmosets and squirrel monkeys are susceptible to HAV.[8, 15, 18, 20, 22, 24, 29, 36]

HAV-induced disease in non-human primates resembles human disease, but is usually milder, or subclinical, followed by complete recovery.[8, 18, 20, 29]

HAV can be transmitted experimentally to these animals, but the presence of anti-HAV antibody in the sera of newly captured monkeys shows that infection may also spread in the natural habitat of non-human primates. HAV isolates from several naturally infected monkeys were shown to represent strict simian HAV strains, closely related antigenically to human HAV strains.[8, 14, 20, 22, 24]

A molecular comparison of the human HM175 and the simian PA21 and PA33 strains of HAV has shown that, despite major divergence at the nucleotide level (>10%), the viruses share immunodominant neutralization epitopes. Infection of owl monkeys with either virus provides high, although incomplete (mild symptoms, relapsing hepatitis) protection against later intravenous challenge with the other virus.[14, 24]

Well documented is the natural transmission of human HAV from experimentally infected animals to humans. Still unknown is the susceptibility of humans to true simian HAV strains.

If it could be shown that simian strains do not induce disease in humans despite virus replication and subsequent seroconversion, simian strains might be used as live, attenuated vaccines.

If, on the other hand, HAV-immune people challenged with simian HAV strains developed signs of hepatitis,

even a global immunization programme could never achieve the eradication of HAV, because monkeys would constantly represent a natural reservoir of virus.

Risk groups

Certain groups can be defined as high risk for contracting HAV :[18, 21, 23, 41, 45]

- people in household/sexual contact with infected persons
- medical and paramedical personnel in hospitals
- international travellers from developed countries to regions of the world where HAV is endemic (3/1000 to 20/1000 people per month's stay abroad)
- persons living in regions with endemic hepatitis A
- persons residing in areas where extended community outbreaks exist
- preschool children attending day-care centres, their parents and siblings
- day-care centre employees
- residents and staff of closed communities (institutions)
- refugees residing in temporary camps following catastrophes
- homosexually active men
- injecting drug users using unsterilized injection needles
- persons with clotting factor disorders
- persons with chronic liver disease
- food-service establishments/food handlers
- persons working with non-human primates

Risk factors remain unidentified in as much as 50% of hepatitis A cases.[21, 45]

Hepatitis A is contracted at least 100 times more frequently than typhoid fever or cholera.

Persons falling into any of the above mentioned categories should consider being vaccinated as a preventive measure.

Surveillance and Control

Surveillance and control procedures should include

- providing safe drinking water and proper disposal of sanitary waste
- monitoring water beds where shellfish are harvested
- monitoring disease incidence
- determining sources of infection
- identifying contacts of case-patients for postexposure prophylaxis
- detecting outbreaks
- containing spread

Endemicity

Geographic areas can be characterized by high, intermediate or low levels of endemicity patterns of HAV infection. The levels of endemicity correlate with hygienic and sanitary conditions of each geographic area.[18, 21, 31, 41, 45]

- *high*: In developing countries with very poor sanitary and hygienic conditions (parts of Africa, Asia and Central and South America), infection is usually acquired during early childhood as an asymptomatic or mild infection. Reported disease rates in these areas are therefore low and outbreaks of disease are rare. Reported disease incidence may reach 150 per 100 000 per year.

- *intermediate*: In developing countries, countries with transitional economies and some regions of industrialized countries where sanitary conditions are variable (Southern and Eastern Europe, some regions in the Middle East), children escape infection in early childhood. Paradoxically, these improved economic and sanitary conditions may lead to a higher disease incidence, as infections occur in older age groups, and reported rates of clinically evident hepatitis A are higher.

- *low*: In developed countries (Northern and Western Europe, Japan, Australia, New Zealand, USA, Canada) with good sanitary and hygienic conditions, infection rates are generally low. In countries with very low HAV infection rates, disease may occur among specific risk groups such as travellers.

Worldwide endemicity of HAV infection

HAV ENDEMICITY	REGIONS BY EPIDEMIOLOGICAL PATTERN	AVERAGE AGE OF PATIENTS (YEARS)	MOST LIKELY MODE OF TRANSMISSION
Very high	Africa, parts of South America, the Middle East and of south-east Asia	under 5	- person-to-person - contaminated food and water
High	Brazil's Amazon basin, China and Latin America	5-14	- person-to-person - outbreaks/contaminated food or water
Intermediate	Southern and Eastern Europe, some regions of the Middle East	5-24	- person-to-person - outbreaks/contaminated food or water
Low	Australia, USA, Western Europe	5-40	- common source outbreaks
Very low	Northern Europe and Japan	over 20	- exposure during travel to high endemicity areas, uncommon source

Worldwide endemicity of HAV infection[5, 11, 42, 44, 45]

Incidence/Epidemiology

Hepatitis A occurs sporadically and epidemically worldwide, with a tendency to cyclic recurrences.[22]

Epidemics are uncommon in developing countries where adults are generally immune. Improved sanitation and hygiene conditions in different parts of the world leave large segments of the population susceptible to infection, and outbreaks may result whenever the virus is introduced.[22, 31, 37]

Common-source epidemics, related to contaminated food or water, may evolve explosively, as did the largest mollusc-linked epidemic in Shanghai, in 1988, involving about 300 000 people.[31]

Worldwide, HAV infections account for 1.4 million cases annually.[45]

Estimated number of cases per continental region

REGION	1990 POPULATION (IN MILLIONS)	INCIDENCE (PER 100,000 PER YEAR)	CASES (PER YEAR)
North America	275	10	28,000
Central and South America	453	20-40	162,000
Europe	791	5-60	278,000
Africa and Middle East	827	20-60	251,000
Asia	2893	10-30	676,000
Oceania	28	15-30	5,000
Total			1,399,000

From: Hadler SC. Global impact of hepatitis A virus infection changing patterns. In: Hollinger FB, Lemon SM, and Margolis HS, eds. Viral Hepatitis and Liver Disease. Baltimore, Williams & Wilkins, 1991:14-20, with permission (http://lww.com).

Trends

As nations develop public sanitation, the age at which individuals will become infected is delayed until adulthood, at which time the likelihood of developing symptomatic illness is considerably higher.[16, 18, 31]

In the United States, nationwide outbreak cycles appear every decade, as observed in 1961, 1971 and 1989.

Hepatitis A appears to follow a minor cyclic phase, with a peak occurring during fall and winter, possibly as a result of exposure during summer holidays spent in endemic countries. Smaller epidemics are present in different parts of the world, with cases increasing slightly during the past several years. Decreasing are cases in Greece and Italy.[28, 31]

The rate in males is about 20% higher than in females.[18]

Costs

Although most infected persons recover completely and a significant proportion remain asymptomatic, HAV infection causes considerable morbidity and mortality and imposes a large economic burden throughout the world.[7, 43]

On average, adults miss 30 days of work. Young children tend to suffer only flu-like symptoms, if any, but

infection of children can initiate and perpetuate community-wide outbreaks.
Both medical treatment and work loss account in the United States for an estimated annual US$ 500 million (1997) costs for 63 500 cases of acute hepatitis A. For each hospitalized case, medical care costs sum up to about US$ 6900.[7]

Worldwide, an estimated 1.4 million cases of acute hepatitis A annually cost US$ 1.5 to US$ 3 billion.[4, 18, 40]

An HAV antibody screening test and its subsequent evaluation are estimated to cost US$ 43 per case.[43]

The costs of vaccination are estimated to be US$ 40 for one 720 EL.U. dose plus US$ 15 for the administration. Two doses are required for a complete vaccination.[43]

For passive immunization, the purchase and administration of one IG dose is estimated at US$ 41.[43]

Cost-effective analyses performed in Ireland showed that where HAV immunity is 45% or less, vaccination is the strategy of choice, and when immunity is greater than 45%, then screening followed by vaccination should be used.[34]

Immune prophylaxis

Until recently, passive immunization with pooled IG was the only option available for preventing hepatitis A. HAV research has led to the development of inactivated vaccines. Their use is being encouraged and preferred to the administration of IG for preexposure prophylaxis when repeated exposure is anticipated.[21]

- *passive immunization:*

The administration of IG can reduce the incidence of hepatitis A up to 90%, and it is most effective if given before exposure. Its use is declining now that HAV vaccines are being used more widely.[21]

IG is still used for postexposure prophylaxis. If administered within two weeks of exposure it will either prevent development or reduce the severity of the disease.[21, 22, 39]

Passive immunization is safe for adults and children, pregnant or lactating women and immunosuppressed persons, but it only provides a limited duration of protection after a single IG dose of 100 IU (6 months), leaving susceptibles available for infection following another exposure.

Because of its short duration of action, IG must be readministered on a regular basis to maintain its effectiveness and ensure continuous protection. It is therefore expensive, logistically complicated and unreliable to supply long-term protection, and considered obsolete, except for situations in which immediate protection is required. Moreover, IG can interfere with immune response to live, attenuated vaccines (measles, mumps, rubella (MMR) and varicella). The administration of MMR should be delayed at least 3 months and 5 months for varicella after administration of IG. On the other hand, IG should not be administered within 2 weeks after administration of live, attenuated vaccines.

- *active immunization:*

At least four inactivated vaccines (Havrix®, Vaqta®, Epaxal®, and Avaxim®) are presently commercially

available in some parts of the world.

Inactivated HA vaccines are safe, highly immunogenic, and provide long-term protection from HAV infection (20 years). They can be administered simultaneously with a number of other vaccines (diphtheria, polio, tetanus, oral typhoid, cholera, Japanese encephalitis, rabies, yellow fever and hepatitis B) without affecting the rates of seroconversion.[12]

Hepatitis A is the most common immunization-preventable infection in travellers.[41, 47]

Recommendations for use of hepatitis A vaccine and IG

- *preexposure prophylaxis*

Hepatitis A vaccination provides preexposure protection from HAV infection. It is recommended for persons who are at increased risk for infection and for any person wishing to obtain immunity.

Persons who seek immunological protection, but are allergic to vaccine components should receive IG. The administration must be repeated if protection is required for periods exceeding 5 months. For persons who require repeated IG, screening of their immune status is useful to avoid unnecessary doses of IG.

- *postexposure prophylaxis*

Persons who have been exposed to HAV and who have not previously been vaccinated should be administered a dose of IG (0.02ml/kg) within two weeks of exposure.[39] Persons who have received a dose of hepatitis A vaccine at least 2 weeks before exposure to HAV do not need IG.

Mass postexposure vaccination to contain the spread of HAV in established outbreaks has been well documented and proven efficacious in ceasing emerging epidemics.[21]

Serologic screening of contacts of infected individuals for anti-HAV before they are given IG is not recommended because screening is more costly than IG and would delay its administration.

The prospective duration of antibody persistence can be estimated to last at least 20 years. However, a booster vaccination after 10 years is recommended for protection, as long as no long-term follow-up data are available.[19, 21, 27]

Recommended doses of IG for hepatitis A preexposure and postexposure prophylaxis

SETTING	DURATION OF COVERAGE	IG DOSE
preexposure	short-term (1 - 2 months)	0.02 ml/kg
	long-term (3 - 5 months)	0.06 ml/kg°
postexposure		0.02 ml/kg

- Doses should be given as intramuscular injections into deltoid or gluteal muscle. For children <2 years of age, injections should be given into anterolateral thigh muscle

- Whenever possible, HAV vaccination should be the procedure of choice.

° repeat every 5 months if continued exposure to HAV occurs [9]

Vaccines

The use of gamma globulin has provided passive, short-term protection. Vaccines give active and long lasting protection against hepatitis A.[16, 19, 23, 27]

- *live, attenuated HAV vaccine*

Inexpensive, live, attenuated vaccines have been produced in China, and millions of Chinese may have been vaccinated, although little information about these preparations is currently available. The H2-strain vaccine does not induce seroconversion if given orally, but nearly all of the individuals that were given the vaccine subcutaneously developed antibodies. This attenuated HAV is not transmitted orally although it is shed in stools in little amounts. The vaccine gave 100% protection against HAV infection during a 4 year period at 11 primary schools.[4, 18, 21, 28, 40]

- *inactivated HAV vaccines*

The first inactivated HAV vaccine (Havrix®, SmithKline Beecham) became available for i.m. injection in Europe in 1991 and was approved in the United States in 1995. The second inactivated vaccine came in 1995 (Vaqta®, Merck). Both are whole-virus preparations, produced by growth of attenuated HAV strains in cell culture, inactivated with formalin, adsorbed to aluminium as adjuvant. Havrix® is preserved in 2-phenoxyethanol. Both vaccines are highly effective and provide seroconversion rates of more than 99.4% when given as a single primary immunisation, followed by a booster dose 6-12 months later.[18, 19, 21, 23, 27, 45]

A third vaccine (Epaxal®, Berna) developed in Switzerland and currently marketed in Switzerland and Argentina, incorporates immunogenic formalin-inactivated HAV particles within immunopotentiating reconstituted influenza virosomes that facilitate antigen delivery to immunocompetent cells.[3, 18, 21, 26, 33, 45]

Another inactivated vaccine (Avaxim®, Pasteur Mérieux) has given excellent results since its introduction in France, the Netherlands, Sweden and the United Kingdom in 1997.[45]
A combined hepatitis A and B vaccine (Twinrix®, SmithKline Beecham) has been introduced in Australia, Canada and some countries in Europe in 1997. In its adult formulation it contains 720 ELISA Units (EL.U.) of hepatitis A antigen (Havrix®) and 20 ìg of hepatitis B surface antigen (Engerix®-B) adsorbed onto aluminium salts.[45] Twinrix® is licensed for use in children aged 1 year or older in several countries and is given as a 3-dose series, using a 0, 1, 6 months schedule. The immunogenicity of the combined vaccine has been compared to the immunogenicity of simultaneously or separately applied single vaccines. The results of the study recommend the use of the combined vaccine for subjects at risk for both hepatitis A and hepatitis B.[13]

In the United States, IG is still recommended for protection from HAV infection in children less than 2 years of age, because residual anti-HAV passively acquired from the mother may interfere with vaccine immunogenicity.[21]

If not specified otherwise, manufacturers suggest that paediatric formulations contain half the antigenic mass of the adult formulation and are given to children and adolescents between 1 and 18 years of age.
Immunization priorities differ between countries, as do vaccination schedules, local production capabilities, and demands for specific vaccine combinations.

The systematic use of Havrix® in Alaska in 1996, covering at least 80% of eligible persons, indicates that the vaccine can efficiently stop established outbreaks and prevent epidemics of hepatitis A in communities where cases of hepatitis A are documented.[21, 30, 45]

Havrix® is the only vaccine specifically licensed for active immunization against the hepatitis A virus in chronic liver disease patients.

Recommended dosages of available vaccines

HAVRIX® (SMITHKLINE BEECHAM BIOLOGICALS)					
Group	**Age (years)**	**Dose (ELISA Units, EL.U.)**	**Volume**	**No. Doses**	**Schedule (months)**
Children and adolescents	2-19	720 EL.U.	0.5 ml	2	0, 6-12
Children and adolescents	1-18	360 EL.U. (US$ 19.50)°	0.5 ml	3	0, 1, 6-12
adults	>18	1440 EL.U. (US$ 56.90)°	1.0 ml	2	0, 6-12

VAQTA® (MERCK & CO., INC.)					
Group	**Age (years)**	**Dose (Units, U)**	**Volume**	**No. Doses**	**Schedule (months)**
Children and adolescents	2-17	25 U	0.5 ml	2	0, 6-18
adults	>17	50 U	1.0 ml	2	0, 6

0 months represents timing of the initial dose. Subsequent numbers indicate months after the initial dose.
° Prices are the average wholesale costs per single-unit dose in the United States.[9]

For travellers who seek medical advice less than 2 weeks before travelling, a double dose is recommended (two injections, single dose; or one injection, double dose). This induces antibodies in over 90% of individuals within 2 weeks, and will most probably protect against infection. Alternatively, a dose of IG (0.02 ml/kg body weight) may be given with the first dose of vaccine.

When hepatitis A vaccine is administered concomitantly with pooled IG for immediate protection, separate syringes and different sites must be used.

Persons allergic to vaccine components should follow the recommendations for the use of IG.

Persons who have anti-HAV from prior infection do not need to be vaccinated, but do not react adversely to immunization.

Studies for the development of safe and efficacious live-attenuated vaccines are currently in progress.

HAV vaccines are stable and can be stored for at least two years at 4°C without loss of immunogenicity.[21]

Vaccine safety

Havrix®, Vaqta®, Avaxim®, Epaxal® and Twinrix® have excellent safety profiles and are highly immunogenic in humans.[3, 18, 19, 32] Nearly 100% of vaccinees will develop protective levels of antibody within 1 month of the first dose of vaccine.

Side effects are local, of low intensity and short duration, involving a generally clinically insignificant soreness at the injection site.

Safety of the vaccines has not been determined during pregnancy.

Because the available vaccines are inactivated, no special precautions need to be taken in vaccination of HIV-1 positive or otherwise immunocompromised persons, although they may be less responsive.[21]

Vaccination strategies

The best vaccination strategy for a region depends on the epidemiology of HAV, the risk groups involved, the duration of protection, the possibility of postexposure protection, and the cost of the intervention.[45]

Groups at high risk of HAV infection as a result of behaviour, lifestyle or occupation should be the primary target of a hepatitis A vaccination programme.[45]

It is important to note that for many cases of hepatitis A risk factors and sources of infection cannot be identified. Immunization programmes directed only to high risk groups would miss those with unidentified risks, and would therefore not reduce the impact of the disease or eliminate hepatitis A.[17]

In most developing countries hepatitis A is not a real public health priority, since it is acquired in early childhood when infections are usually asymptomatic. These countries do not at present need to consider universal hepatitis A immunization programmes.[17]

Prevention and Treatment

Since antivirals have never been as successful for the treatment of viral infections as antibiotics have been for the treatment of bacterial infections, prevention of viral diseases remains the most important weapon for their control.

Prevention

As almost all HAV infections are spread by the faecal - oral route, good personal hygiene, high quality standards for public water supplies and proper disposal of sanitary waste have resulted in a low prevalence of HAV infections in many well developed societies.[18, 22]

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.[18]

For preexposure protection, the use of hepatitis A vaccines instead of IG is now highly recommended. Immunization should be a priority for persons at increased risk of acquiring hepatitis A.

For postexposure prophylaxis of non-vaccinated people, the passive administration of IG can modify the symptoms of infection, provided it is given within 2 weeks of exposure.[21, 40]

No special precautions are demanded for vaccinated persons.

Universal immunization would successfully control hepatitis A, although at present, high costs and limited availability of vaccines preclude such a recommendation.[17, 21, 23]

Eradication, however, can only be achieved through universal vaccination policies as long as HAV is not endemic in primates.

Treatment

As no specific treatment exists for hepatitis A, prevention is the most effective approach against the disease.[4, 40]

Therapy should be supportive and aimed at maintaining adequate nutritional balance (1 g/kg protein, 30-35 cal/kg). There is no good evidence that restriction of fats has any beneficial effect on the course of the disease. Eggs, milk and butter may actually help provide a correct caloric intake. Alcoholic beverages should not be consumed during acute hepatitis because of the direct hepatotoxic effect of alcohol. On the other hand, a modest consumption of alcohol during convalescence does not seem to be harmful. Hospitalization is usually not required.[18, 40]

Adrenocortical steroids (corticosteroids) and IG are of no value in acute, uncomplicated hepatitis A, since they have no effect on the resolution of the underlying disease.[18]

Antiviral agents have no beneficial clinical effect because a specific antiviral agent is not available and hepatic injury appears to be immunopathologically mediated.[40]

Patients who are taking oral contraceptives do not need to discontinue their use during the course of the disease.

Referral to a liver transplant centre is appropriate for patients with fulminant hepatitis A, although the identification of patients requiring liver transplantation is difficult. A good proportion of patients (60%) with grade 4 encephalopathy will still survive without transplantation. Temporary auxiliary liver transplantation for subacute liver failure may be a way to promote native liver regeneration.[6, 18, 40]

Guidelines for epidemic measures

1. Determination of mode of transmission, whether person-to-person or by common vector (vehicle).

2. Identification of the population exposed to increased risk of infection.
   Elimination of common sources of infection.

3. Improvement of sanitary and hygienic practices to eliminate faecal contamination of food and water.

4. Hepatitis A vaccination has been shown to be effective in controlling outbreaks of infection in communities that have high or intermediate rates of infection, provided a sufficient percent of the target population is reached.[30, 45]

5. Passive immunization provides temporary protection, but it is not effective in controlling HAV on a community level.

Future considerations

Appropriate vaccine doses and schedules in the first two years of life need to be determined to overcome the reduced immune response observed among infants who have passively acquired maternal anti-HAV.

The duration of protection following a single dose of vaccine should be investigated.

Combination vaccines that integrate hepatitis A vaccine into existing childhood vaccination schedules need to be determined.

Most effective vaccination strategies for interrupting and preventing community wide outbreaks need to be defined.

Countries are encouraged to carry out studies addressing the cost-effectiveness of HAV prevention strategies to determine the feasibility of vaccination programmes.[7, 34]

The development of attenuated HAV vaccines capable of offering cost, production and administration advantages should be considered.

An assay to detect antibody to nonstructural proteins may serve, in future, to distinguish between natural infection and vaccine-induced antibody formation.[23, 35, 39]

Glossary

adjuvant any substance which, when mixed with an antigen, increases the immune response to that antigen.[1]

albumin a water soluble protein. Serum albumin is found in blood plasma and is important for maintaining plasma volume and osmotic pressure of circulating blood. Albumin is synthesized in the liver. The inability to synthesize albumin is a predominant feature of chronic liver disease.

alkaline phosphatase any of group of phosphatases showing activity at alkaline pH, which are normally measured collectively in blood serum. Serum levels are elevated in various conditions, among which hepatobiliary disorders.

ALT alanine aminotransferase an enzyme that interconverts L-alanine and D-alanine. It is a highly sensitive indicator of hepatocellular damage. When such damage occurs, ALT is released from the liver cells into the bloodstream, resulting in abnormally high serum levels. Normal ALT levels range from 10 to 32 U/l; in women, from 9 to 24 U/l. The normal range for infants is twice that of adults.

antibody a protein molecule formed by the immune system which reacts specifically with the antigen that induced its synthesis. All antibodies are immune globulins.[1]

antigen any substance which can elicit in a vertebrate host the formation of specific antibodies or the generation of a specific population of lymphocytes reactive with the substance. Antigens may be protein or carbohydrate, lipid or nucleic acid, or contain elements of all or any of these as well as organic or inorganic chemical groups attached to protein or other macromolecule. Whether a material is an antigen in a particular host depends on whether the material is foreign to the host and also on the genetic makeup of the host, as well as on the dose and physical state of the antigen.[1]

AST aspartate aminotransferase the enzyme that catalyzes the reaction of aspartate with 2-oxoglutarate to give glutamate and oxaloacetate. Its concentration in blood may be raised in liver and heart diseases that are associated with damage to those tissues. Normal AST levels range from 8 to 20 U/l. AST levels fluctuate in response to the extent of cellular necrosis.[1]

bilirubin is the chief pigment of bile, formed mainly from the breakdown of haemoglobin. After formation it is transported in the plasma to the liver to be then excreted in the bile. Elevation of bile in the blood causes jaundice.[46]

capsid the protein coat of a virion, composed of large multimeric proteins, which closely surrounds the nucleic acid.[1]

cholestasis impairment of bile flow at any level from the canaliculus to the duodenum. The clinical condition resulting therefrom, characterised by icterus and pruritus, is due to the accumulation in blood and tissues of substances normally secreted in bile, particularly bilirubin, bile salts, and cholesterol.[1]

complete blood count chemical analysis of various substances in the blood performed with the aim of a)

assessing the patient's status by establishing normal levels for each individual patient, b) preventing disease by alerting to potentially dangerous levels of blood constituents that could lead to more serious conditions, c) establishing a diagnosis for already present pathologic conditions, and d) assessing a patient's progress when a disturbance in blood chemistry already exists.

cytopathic effects include morphological changes in the cell appearance (rounding up of cells), agglutination of red blood cells (haemagglutination assay with influenza-virus), zones of cell lysis on monolayers of tissue culture or finally immortalization of animal cell lines (foci formation).

encephalopathy an acute reaction of the brain to a variety of toxic or infective agents, without any actual inflammation such as occurs in encephalitis.[1]

endemic continuously prevalent in some degree in a community or region.[46]

enzyme any protein catalyst, i.e. substance which accelerates chemical reactions without itself being used up in the process. Many enzymes are specific to the substance on which they can act, called substrate. Enzymes are present in all living matter and are involved in all the metabolic processes upon which life depends.[46]

epidemic an outbreak of disease such that for a limited period a significantly greater number of persons in a community or region suffer from it than is normally the case. Thus an epidemic is a temporary increase in prevalence. Its extent and duration are determined by the interaction of such variables as the nature and infectivity of the casual agent, its mode of transmission and the degree of preexisting and newly acquired immunity.[46]

epitope or antigenic determinant. The small portion of an antigen that combines with a specific antibody. A single antigen molecule may carry several different epitopes.[1]

fulminant describes pathological conditions that develop suddenly and are of great severity.[46]

genotype the genetic constitution of an individual

hepatocytes are liver cells.[1]

humoral pertaining to the humors, or certain fluids, of the body.[1]

icterus jaundice.[1]

IgA antibodies IgA has antiviral properties. Its production is stimulated by aerosol immunizations and oral vaccines.

IgG antibodies IgG is the most abundant of the circulating antibodies. It readily crosses the walls of blood vessels and enters tissue fluids. IgG also crosses the placenta and confers passive immunity from the mother to the fetus. IgG protects against bacteria, viruses, and toxins circulating in the blood and lymph.

IgM antibodies IgMs are the first circulating antibodies to appear in response to an antigen. However, their concentration in the blood declines rapidly. This is diagnostically useful, because the presence of IgM usually indicates a current infection by the pathogen causing its formation. IgM consists of five Y-shaped

monomers arranged in a pentamer structure. The numerous antigen-binding sites make it very effective in agglutinating antigens. IgM is too large to cross the placenta and hence does not confer maternal immunity.

Immune globulin (IG): is a sterile preparation of concentrated antibodies (immune globulins) recovered from pooled human plasma processed by cold ethanol fractionation. Only plasma that has tested negative for a) hepatitis B surface antigen (HBsAg), b) antibody to human immunodeficiency virus (HIV), and c) antibody to hepatitis C virus (HCV) is used to manufacture IG. IG is administered to protect against certain diseases through passive transfer of antibody. The IGs are broadly classified into five types on the basis of physical, antigenic and functional variations, and labelled respectively IgM, IgG, IgA, IgE and IgD.

immunocompetent capable of responding immunologically to an antigen, as by producing antibodies or by developing cell-mediated immunity.[1]
immunodominant describing those epitopes in a molecule, or those components in an antigenic mixture, to which an immune response is produced preferentially.[1]

immunogenic capable of eliciting an immune response.

incidence the number of cases of a disease, abnormality, accident, etc., arising in a defined population during a stated period, expressed as a proportion, such as x cases per 1000 persons per year.[1]

interferon a class of proteins processing antiviral and antitumour activity produced by lymphocytes, fibroblasts and other tissues. They are released by cells invaded by virus and are able to inhibit virus multiplication in noninfected cells. Interferon preparations have been shown to have some clinical effect as antiviral agents. The preparations so far available have produced side effects, such as fever, lassitude, and prostration, not dissimilar from those accompanying acute virus infection itself.[46]

jaundice a yellow discoloration of the skin and mucous membranes due to excess of bilirubin in the blood, also known as icterus.[46]

lymphocyte a leukocyte of blood, bone marrow and lymphatic tissue. Lymphocytes play a major role in both cellular and humoral immunity, and thus several different functional and morphologic types must be recognized, i.e. the small, large, B-, and T-lymphocytes, with further morphologic distinction being made among the B-lymphocytes and functional distinction among T-lymphocytes.[1]

monoclonal antibodies preparations containing only one kind of antibody molecules, with specificity for a single antigen. Monoclonal antibodies are of great therapeutic and diagnostic potential.[46]

necrosis death of tissue.[46]

peptide a compound of two or more amino acids linked together by peptide bonds.[46]

pleomorphic distinguished by having more than one form during a life cycle.[1]

prevalence the number of instances of infections or of persons ill, or of any other event such as accidents, in a specified population, without any distinction between new and old cases.[46]

prodrome an early symptom suggestive of the onset of an attack or disease; a premonitory event.[1]

prophylaxis the prevention of disease, or the preventive treatment of a recurrent disorder.[46]

protein large molecule made up of many amino acids chemically linked together by amide linkages. Biologically important as enzymes, structural protein and connective tissue.
prothrombin time a test used to measure the activity of clotting factors I, II, V, VII, and X. Deficiency of any of these factors leads to a prolongation of the prothrombin time. The test is basic to any study of the coagulation process, and it helps in establishing and maintaining anticoagulant therapy.

pruritus itching

self-limited denoting a disease that tends to cease after a definite period; e.g., pneumonia.[2]

seroconversion the production in a host of specific antibodies as a result of infection or immunization. The antibodies can be detected in the host's blood serum following, but not preceding, infection or immunization.[1]
serotype a subdivision of a species or subspecies distinguishable from other strains therein on the basis of antigenic character.[2]

serum is the clear, slightly yellow fluid which separates from blood when it clots. In composition it resembles blood plasma, but with fibrinogen removed. Sera containing antibodies and antitoxins against infections and toxins of various kinds (antisera) have been used extensively in prevention or treatment of various diseases.[46]

titre a measure of the concentration or activity of an active substance.

urobilinogen also called stercobilinogen. A colourless, reduced form of stercobilin, in which the pyrrole rings are joined by $-CH_2-$ groups. It is oxidized by air to the coloured stercobilin.[1]

vaccine an antigenic preparation used to produce active immunity to a disease to prevent or ameliorate the effects of infection with the natural or "wild" organism. Vaccines may be living, attenuated strains of viruses or bacteria which give rise to inapparent to trivial infections. Vaccines may also be killed or inactivated organisms or purified products derived from them. Formalin-inactivated toxins are used as vaccines against diphtheria and tetanus. Synthetically or genetically engineered antigens are currently being developed for use as vaccines. Some vaccines are effective by mouth, but most have to be given parenterally.[1, 46]

vaccinee person receiving a vaccine

viremia the presence of viruses in the blood.

virion a structurally complete virus, a viral particle.[1]

virosomes immunopotentiating reconstituted influenza virosomes (IRIVs) are safe, efficacious and easily prepared carrier systems for small virion particles, such as HAV. IRIVs are spherical, unilamellar vescicles, with a diameter of about 150 nm, that combine components like haemagglutinin, neuraminidase and phospholipids of influenza virus and adsorbed HAV particles. The essential feature of IRIVs is that as well as the HAV antigen, their surface contains the fusion-inducing component haemagglutinin, which facilitates antigen delivery to immunocompetent cells. Most adults have been exposed to influenza haemagglutinin, and so IRIVs recruit primed cells leading to a rapid immune response.[26]

virus any of a number of small, obligatory intracellular parasites with a single type of nucleic acid, either DNA or RNA and no cell wall. The nucleic acid is enclosed in a structure called a capsid, which is composed of repeating protein subunits called capsomeres, with or without a lipid envelope. The complete infectious virus particle, called a virion, must rely on the metabolism of the cell it infects. Viruses are morphologically heterogeneous, occurring as spherical, filamentous, polyhedral, or pleomorphic particles. They are classified by the host infected, the type of nucleic acid, the symmetry of the capsid, and the presence or absence of an envelope.[1]

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