

# Essential Drugs

## Viral hepatitis

Viral hepatitis, which is probably the most common of all serious viral diseases, comprises several clinically similar infections that are etiologically and epidemiologically distinct. Hepatitis A virus causes an acute, usually self-limiting infection that can cause a variable degree of liver damage but does not cause chronic disease. Hepatitis B virus infection can also present as an acute infection, but many patients, and particularly young children, become chronic carriers of the virus. They are important in the transmission of the disease and many ultimately die from chronic liver disease and primary liver cancer. Hepatitis C, formerly referred to as parenterally-transmitted non-A, non-B hepatitis, is responsible for most cases of blood transmitted hepatitis. Hepatitis E virus causes large epidemics of waterborne hepatitis in developing countries as well as sporadic disease and has a high mortality rate in pregnant women. Delta hepatitis is caused by an "incomplete" RNA virus — or delta agent — that replicates only in the presence of hepatitis B virus and augments the severity of the primary infection.

### Hepatitis A

The hepatitis A virus (HAV) is usually transmitted from person to person or through faecal contamination of water or food and, particularly, contaminated shellfish. It is also transmitted by sexual contact and, very rarely, by transfusion of infected blood.

Sporadic cases occur everywhere but, where sanitation is inadequate, entire communities become infected during childhood. The age of infection tends to shift progressively to older children and young adults as sanitary conditions improve.

The incubation period ranges from 14 to 45 days. The virus replicates only in the liver and is excreted via the biliary tract into the faeces. The viral load in the faeces is greatest during the last 1–2 weeks of the incubation period, before symptoms appear. Thereafter, it decreases substantially. Viraemia is also detectable late in the incubation period and sometimes during the first few days of the clinical illness.

The resulting liver damage is probably immunologically mediated. The initial phase of intense viral replication is unaccompanied by evidence of liver dysfunction. Biochemical and clinical evidence of such injury develops in parallel with the formation of a specific antibody (IgM anti-HAV) and at a time of decreasing viral replication. This antibody is usually no longer detectable after 2–6 months, but IgG anti-HAV usually persists for life, providing protection against reinfection.

The disease varies considerably in severity. Mild infections with few or no symptoms are common in children, but death occasionally results from fulminant hepatitis. Children under 6 years generally experience no more than transient malaise, nausea, vomiting and diarrhoea; only about 10% become icteric. Older children and adults develop the classical symptoms of malaise, nausea, vomiting and loss of appetite, and more than 3 in 4 become jaundiced. Chronic carriers have not been identified.

### Control

Prevention is primarily dependent upon maintaining satisfactory standards of sanitation and personal hygiene.

A specific hepatitis A vaccine which provides a high level of long-term protection in travellers and other groups at risk is now available in many countries. However, human immunoglobulin (IgG) remains widely used, both as a cheaper means of providing pre-exposure prophylaxis in travellers to endemic regions, and also to provide post-exposure prophylaxis. Used for the latter purpose, it confers immediate but transient (2–4 months) protection when it is administered within a week or two of exposure. It is of particular value in protecting close household and sexual contacts of confirmed cases and in containing outbreaks of the disease in institutions such as day-care centres for children and homes for the mentally disabled.

### Hepatitis B

Hepatitis B occurs throughout the world and it is hyperendemic in sub-Saharan Africa and south-east Asia. In hyperendemic areas most children

become infected during the first few years of life. Infants born to mothers who are chronic carriers of the disease are at high risk of developing infection during the perinatal period. Transmission *in utero* is rare because the virus does not readily cross the intact placental barrier. In early childhood, transmission readily occurs between siblings and close contacts. Among adults not previously infected, sexual contact and, in some countries, blood transfusion are important modes of transmission. Drug abusers and health workers are at specific risk of inoculation of infected blood.

The clinical course of the acute phase of the infection is similar to that of hepatitis A. Mild, non-icteric illness is common among infants and young children. Clinical evidence of liver damage, including jaundice, is more common among older children and adults. Rarely, the disease runs a fulminant and fatal course. The majority of infected infants and young children become chronic carriers of the virus. The carrier state is considerably less common among individuals first infected later in childhood or as adults. Of an estimated global population of some 300 million chronic carriers it is estimated that 25–30% will ultimately die from chronic hepatitis, cirrhosis or primary hepatocellular carcinoma.

Infection is accompanied by the appearance of several immunological markers. A specific surface antigen (HBsAg) first becomes detectable in the serum approximately 30–60 days after exposure. Surface antigen that remains detectable for more than 6 months is presumptive evidence of chronic infection. Antibodies to the surface antigen, which develop as the acute infection resolves, are responsible for long-term immunity. Specific antibodies to core antigen (anti-HBc) are also detectable for prolonged periods. Hepatitis Be antigen (HBeAg) correlates with high rates of viral replication and with infectivity. Antibody to the e antigen (anti-HBe) becomes detectable following acute infections and frequently persists in the sera of carriers once HBeAg has disappeared.

### Prevention

All infants should be vaccinated with hepatitis B vaccine shortly after birth. When administered during the first years of life by various regimens involving 3 or 4 doses given over a period of several months, this vaccine is highly effective in protecting children from persistent infection over periods as long as 10 years.

In communities exposed to lesser risk of infection, vaccination should also be given to individuals at relatively high risk. These include intravenous drug abusers, homosexuals, persons in household contact with a chronic carrier, patients requiring chronic haemodialysis and health workers frequently in contact with blood.

Passive vaccination with hepatitis B immunoglobulin may be usefully combined with hepatitis B vaccination to provide immediate as well as longer-term protection to individuals accidentally exposed to infected blood, to neonates born to an infected mother, or following sexual contact with an infected person.

Vital measures to prevent parenteral transmission of the virus include effective sterilization of needles and syringes, and screening of donated blood to exclude units containing hepatitis B surface antigen.

The use of alpha and beta interferons is being explored in the treatment of selected patients with chronic hepatitis B. However, their modest efficacy and high cost preclude their routine use in many countries at present.

### Hepatitis C

Hepatitis C is now recognized as the major cause of non-epidemic, non-A, non-B hepatitis in most countries. Within the USA this organism is believed to be responsible for more than 90% of post-transfusion hepatitis infections. Drug abusers and dialysis patients are also at risk. Most of the acute infections are anicteric and are characterized only by fatigue or anorexia. Up to 80% of infections, however, result in chronic hepatitis, and it is estimated that at least 20% of these chronic carriers ultimately develop cirrhosis and, among these, many subsequently develop hepatocellular carcinoma.

Blood screening test-kits containing cloned recombinant viral proteins have been developed to detect antibody to the virus in serum or plasma. These are more sensitive than the indirect markers of infection – including alanine amino-transferase levels and antibody to hepatitis B core antigen – already used for this purpose. However, their high cost precludes their use in many developing countries.

In the absence of these screening tests the disease can only be diagnosed by exclusion of hepatitis A and B, and other infectious agents that cause diffuse inflammatory changes throughout the liver.

There is as yet no specific treatment or vaccine for this disease. Preliminary studies with alfa and beta interferons have provided results of some promise, with approximately 25% of patients showing sustained remission.

## Hepatitis E

A recently identified organism, hepatitis E virus, is responsible for highly prevalent epidemic and sporadic waterborne infections that occur in parts of Asia, North and West Africa, and Central America. These cases are characterized by an acute hepatitis which sometimes becomes fulminant, and which is associated with a high fatality rate. Pregnant women are at particular risk of developing fulminant hepatitis and death typically occurs during the third trimester. Control — as with other types of waterborne hepatitis viruses — is largely dependent upon effective sanitation and a clean water supply.

## Delta hepatitis

Delta hepatitis is caused by an RNA virus which is dependent upon the hepatitis B virus for its replication. It is transmitted by inoculation or transfusion of infected blood and, less frequently, by sexual contact. The surface antigen of the hepatitis B virus envelops the infectious RNA of the delta virus. Infection with both viruses sometimes occurs coincidentally, causing a relatively severe infection which, in non-fatal cases, is self-limiting. Superinfection in a chronic hepatitis B carrier usually results in a chronic mixed infection and accelerated development of chronic hepatitis.

Clinically, the delta virus frequently intensifies the severity of the hepatic injury. Fulminant hepatitis commonly occurs. This is characterized by sudden onset of high fever, marked abdominal pain, vomiting and jaundice followed by the development of hepatic encephalopathy resulting in deep coma and seizures. Mortality increases with age, and patients over 45 years often succumb either from the acute phase of infection or — in the case of chronic carriers of hepatitis B — from rapidly-progressive cirrhosis within the span of a few years.

## Control

Effective prevention of hepatitis B, using both non-specific measures and vaccines, provides the only available strategy for stemming co-infection with the delta virus. Alfa interferon has been claimed to attenuate the severity of these infections, but only in a minority of patients.

## Hepatitis B vaccine

### *Injection*

Plasma-derived hepatitis B vaccines are prepared from the plasma of human hepatitis B carriers. Such vaccines have been available for more than 10 years and have an outstanding record of safety and efficacy.

Recombinant hepatitis B vaccines are produced by *Saccharomyces cerevisiae* or mammalian cells into which a plasmid containing the gene for hepatitis B surface antigen (HBsAg) has been inserted. Purified HBsAg is obtained by lysing the yeast cells and separating HBsAg from the yeast components by biochemical and biophysical techniques or from the supernatant of mammalian cell cultures.

Both plasma-derived and DNA-recombinant vaccines which meet the WHO requirements are safe and effective and may be used in immunization programmes.

## Uses

To confer active immunity against hepatitis B infection.

WHO recommends that "hepatitis B vaccine should be integrated into national immunization programmes in all countries with a hepatitis B carrier prevalence (HBsAg) of 8% or greater by 1995 and in all countries by 1997. Target groups and strategies may vary with the local epidemiology. When carrier prevalence is 2% or greater, the most effective strategy is incorporation into the routine infant immunization schedules. Countries with lower prevalence may consider immunization of all adolescents as an addition or alternative to infant immunization.\*

In addition, it is recommended that individuals at high risk of infection should be vaccinated. These

\* Recommendations by the WHO Expanded Programme on Immunization in: EPI for the 1990s: WHO/EPI/GEN/92.2

include frequent travellers to endemic areas, all health workers, intravenous drug abusers, homosexuals, household contacts of HBV carriers and haemodialysis patients.

### Dosage and administration

The vaccine should be administered intramuscularly into the deltoid region of the arm. The anterolateral thigh may be a preferable site in infants and neonates. Most countries recommend that three intramuscular doses of vaccine be administered, with the second and third doses given one and six months, respectively, after the first.

Dosage must be made with reference to the manufacturer's data sheet since this varies between products.

In neonates born to HBsAg positive mothers, hepatitis immunoglobulin may be given simultaneously with the vaccine within a few hours of birth.

### Contraindications

Hypersensitivity to any component of the vaccine.

### Precautions

In haemodialysis patients or patients who are immunocompromised, a booster dose of the vaccine may be necessary.

As with all vaccinations, epinephrine should be immediately available if an anaphylactic reaction occurs.

### Use in pregnancy

Inactivated viral vaccines, in general, pose no specific risk to the fetus. The risk of infection with hepatitis B greatly outweighs any untoward effect of the vaccine. It should be administered during pregnancy whenever it is indicated.

### Adverse effects

Hepatitis B vaccine is usually well-tolerated. Mild transient local soreness, erythema and induration at the injection site are the most commonly recorded reactions.

### Storage

Hepatitis B vaccine should be stored between 2 and 8 °C, protected from light. It should not be allowed to freeze.

## Hepatitis B immune globulin

### Injection

Hepatitis B immune globulin is prepared from the plasma of individuals with high titres of antibody to hepatitis B surface antigen (anti-HBs). It contains thiomersal as a preservative and glycine as a stabilizing agent.

### Uses

It is used, as a prophylactic measure, to generate passive immunity to hepatitis B infection in individuals likely to have been exposed to hepatitis B virus or HBsAg-positive materials.

It is administered in combination with hepatitis B vaccine to provide post-exposure prophylaxis in neonates born to HBsAg-positive mothers and in individuals exposed to presumptive percutaneous inoculation of the virus.

### Dosage and administration

*Adults:* 0.06 ml/kg (about 3–5 ml) administered by intramuscular injection into the deltoid muscle or into the anterolateral aspect of the thigh.

### Contraindications

Known hypersensitivity to hepatitis B immune globulin or any component of the finished preparation.

### Precautions

Because of the risk of anaphylaxis, it should be administered with care to individuals with a specific IgA deficiency.

### Use in pregnancy

Because of the serious potential long-term consequences of hepatitis B infection in the neonates, hepatitis B immunoglobulin should be administered to any pregnant woman exposed to risk of transmission.

### Adverse effects

Pain and tenderness may occur at the site of injection.

### Storage

Hepatitis B immunoglobulin should be stored between 2 and 8 °C, protected from light, and should not be allowed to freeze.

## Human immunoglobulin

### *Injection*

Human immunoglobulin is prepared from pools of at least 1000 donations of human plasma; it contains antibody to hepatitis A, measles, mumps, varicella and other viruses that are prevalent in the general population. Injection of human immunoglobulin produces immediate passive immunity to hepatitis A lasting up to 4 months.

A specific hepatitis A immunoglobulin is available in a few countries. However, it is considered too expensive for routine use.

### **Uses**

It is used for post-exposure prophylaxis against hepatitis A in household and sexual contacts of acute cases and in children and staff in day-care centres and institutions for the mentally disabled.

Pre-exposure prophylaxis of hepatitis A for travellers to endemic areas.

### **Dosage and administration**

Post-exposure prophylaxis

*Adults:* 500 mg

*Children:* 250 mg in a single intramuscular injection.

Pre-exposure prophylaxis

*Adults:* 250 mg

*Children:* 125 mg in a single intramuscular injection.

### **Contraindications**

Patients with known specific antibody to immunoglobulin A (IgA).

### **Precautions**

Human immunoglobulin may interfere with the response to live virus vaccines which should therefore be given at least 3 weeks before or 3 months after an injection of human immunoglobulin. For travellers, when insufficient notice is given, this recommended interval may have to be ignored.

### **Adverse effects**

Malaise, chills, fever and rarely anaphylaxis may occur following injection with human immunoglobulin.

### **Storage**

Human immunoglobulin should be stored between 2 and 8° C and should not be frozen.

## Hepatitis A vaccine

### *injection*

Hepatitis A (HA) vaccine is prepared by lysing human diploid cells in which the virus has been grown, purifying by ultrafiltration and inactivating by treatment with formaldehyde. Each 1-ml dose contains not less than 720 ELISA units of hepatitis A viral protein adsorbed onto aluminium hydroxide adjuvant together with 5 mg of 2-phenoxyethanol as preservative.

### **Uses**

The vaccine is used to confer active immunization against infections caused by hepatitis A virus (HAV):

- in travellers to areas where hepatitis A is endemic; and
- in individuals wishing to obtain protection against HAV infection.

The efficacy of HA vaccine in post-exposure and outbreak situations has not yet been established. Research in this area is in progress.

### **Dosage and administration**

Two separate intramuscular injections of 1 ml of vaccine are administered 2–4 weeks apart. Immunity is conferred for up to one year. A 1 ml booster dose 6–12 months after the initial dose is anticipated to provide immunity for up to 10 years. For travellers who seek medical advice less than 2 weeks before travelling, one dose of vaccine given immediately prior to travel is likely to be protective, but further data are required to confirm this. A double dose of the vaccine will induce antibodies in more than 90% of individuals within 2 weeks and will almost certainly protect against infection. Otherwise a dose of immunoglobulin may be administered with the first dose of the vaccine.

### **Contraindications**

Known hypersensitivity to any component of the vaccine.

Severe febrile infections.

### **Precautions**

Appropriate medication for anaphylaxis should always be readily available.

Patients with impaired immunity or those undergoing haemodialysis, may not develop adequate

antibody titres after primary immunization, and may require additional doses of the vaccine.

**Use in pregnancy**

Inactivated viral vaccines, in general, pose no specific risk to the fetus. However, it is prudent, as a general principle, that the vaccine should be administered during pregnancy only to women who are at definite risk of hepatitis A.

**Adverse effects**

Mild reactions, including transient soreness, erythema and induration at the site of injection, have been recorded within the first few days after vaccination.

**Storage**

Hepatitis A vaccine should be stored, protected from light, between 2 and 8° C and must not be frozen.

***The information in this section is subject to consultation prior to definitive publication in the WHO Model Prescribing Information series. Comments, which are invited at this stage, should be referred to:  
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