= Hepatitis B =

Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV) which affects the liver . It can cause both acute and chronic infections . Many people have no symptoms during the initial infection . Some develop a rapid onset of sickness with vomiting , yellowish skin , tiredness , dark urine and abdominal pain . Often these symptoms last a few weeks and rarely does the initial infection result in death . It may take 30 to 180 days for symptoms to begin . In those who get infected around the time of birth 90 % develop chronic hepatitis B while less than 10 % of those infected after the age of five do . Most of those with chronic disease have no symptoms ; however , cirrhosis and liver cancer may eventually develop . These complications result in the death of 15 to 25 % of those with chronic disease .

The virus is transmitted by exposure to infectious blood or body fluids . Infection around the time of birth or from contact with other people 's blood during childhood is the most frequent method by which hepatitis B is acquired in areas where the disease is common . In areas where the disease is rare , intravenous drug use and sexual intercourse are the most frequent routes of infection . Other risk factors include working in healthcare , blood transfusions , dialysis , living with an infected person , travel in countries where the infection rate is high , and living in an institution . Tattooing and acupuncture led to a significant number of cases in the 1980s ; however , this has become less common with improved sterility . The hepatitis B viruses cannot be spread by holding hands , sharing eating utensils , kissing , hugging , coughing , sneezing , or breastfeeding . The infection can be diagnosed 30 to 60 days after exposure . Diagnosis is typically by testing the blood for parts of the virus and for antibodies against the virus . It is one of five known hepatitis viruses : A , B , C , D , and E.

The infection has been preventable by vaccination since 1982 . Vaccination is recommended by the World Health Organization in the first day of life if possible . Two or three more doses are required at a later time for full effect . This vaccine works about 95 % of the time . About 180 countries gave the vaccine as part of national programs as of 2006 . It is also recommended that all blood be tested for hepatitis B before transfusion and condoms be used to prevent infection . During an initial infection , care is based on the symptoms that a person has . In those who develop chronic disease antiviral medication such as tenofovir or interferon may be useful ; however , these drugs are expensive . Liver transplantation is sometimes used for cirrhosis .

About a third of the world population has been infected at one point in their lives , including 240 million to 350 million who have chronic infections . Another 129 million new infections occurred in 2013 . Over 750 @,@ 000 people die of hepatitis B each year . About 300 @,@ 000 of these are due to liver cancer . The disease is now only common in East Asia and sub @-@ Saharan Africa where between 5 and 10 % of adults are chronically infected . Rates in Europe and North America are less than 1 % . It was originally known as serum hepatitis . Research is looking to create foods that contain HBV vaccine . The disease may affect other great apes as well .

= = Signs and symptoms = =

Acute infection with hepatitis B virus is associated with acute viral hepatitis ? an illness that begins with general ill @-@ health , loss of appetite , nausea , vomiting , body aches , mild fever , and dark urine , and then progresses to development of jaundice . It has been noted that itchy skin has been an indication as a possible symptom of all hepatitis virus types . The illness lasts for a few weeks and then gradually improves in most affected people . A few people may have more severe liver disease (fulminant hepatic failure) , and may die as a result . The infection may be entirely asymptomatic and may go unrecognized .

Chronic infection with hepatitis B virus either may be asymptomatic or may be associated with a chronic inflammation of the liver (chronic hepatitis) , leading to cirrhosis over a period of several years . This type of infection dramatically increases the incidence of hepatocellular carcinoma (liver cancer) . Across Europe hepatitis B and C cause approximately 50 % of hepatocellular carcinomas . Chronic carriers are encouraged to avoid consuming alcohol as it increases their risk for cirrhosis

and liver cancer . Hepatitis B virus has been linked to the development of membranous glomerulonephritis (MGN) .

Symptoms outside of the liver are present in 1 ? 10 % of HBV @-@ infected people and include serum @-@ sickness ? like syndrome , acute necrotizing vasculitis (polyarteritis nodosa) , membranous glomerulonephritis , and papular acrodermatitis of childhood (Gianotti ? Crosti syndrome) . The serum @-@ sickness ? like syndrome occurs in the setting of acute hepatitis B , often preceding the onset of jaundice . The clinical features are fever , skin rash , and polyarteritis . The symptoms often subside shortly after the onset of jaundice , but can persist throughout the duration of acute hepatitis B. About 30 ? 50 % of people with acute necrotizing vasculitis (polyarteritis nodosa) are HBV carriers . HBV @-@ associated nephropathy has been described in adults but is more common in children . Membranous glomerulonephritis is the most common form . Other immune @-@ mediated hematological disorders , such as essential mixed cryoglobulinemia and aplastic anemia .

= = Cause = =

= = = Transmission = = =

Transmission of hepatitis B virus results from exposure to infectious blood or body fluids containing blood . It is 50 to 100 times more infectious than HIV . Possible forms of transmission include sexual contact , blood transfusions and transfusion with other human blood products , re @-@ use of contaminated needles and syringes , and vertical transmission from mother to child (MTCT) during childbirth . Without intervention , a mother who is positive for HBsAg has a 20 % risk of passing the infection to her offspring at the time of birth . This risk is as high as 90 % if the mother is also positive for HBeAg . HBV can be transmitted between family members within households , possibly by contact of nonintact skin or mucous membrane with secretions or saliva containing HBV . However , at least 30 % of reported hepatitis B among adults cannot be associated with an identifiable risk factor . Breastfeeding after proper immunoprophylaxis does not appear to contribute to mother @-@ to @-@ child @-@ transmission (MTCT) of HBV . The virus may be detected within 30 to 60 days after infection and can persist and develop into chronic hepatitis B.The incubation period of the hepatitis B virus is 75 days on average , but can vary from 30 to 180 days .

= = = Virology = = =

= = = = Structure = = = =

Hepatitis B virus (HBV) is a member of the hepadnavirus family . The virus particle (virion) consists of an outer lipid envelope and an icosahedral nucleocapsid core composed of protein . These virions are 30 @-@ 42 nm in diameter . The nucleocapsid encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity . The outer envelope contains embedded proteins that are involved in viral binding of , and entry into , susceptible cells . The virus is one of the smallest enveloped animal viruses , and the 42 nm virions , which are capable of infecting liver cells known as hepatocytes , are referred to as " Dane particles " . In addition to the Dane particles , filamentous and spherical bodies lacking a core can be found in the serum of infected individuals . These particles are not infectious and are composed of the lipid and protein that forms part of the surface of the virion , which is called the surface antigens (HBsAg) , and is produced in excess during the life cycle of the virus .

= = = = Genome = = = =

The genome of HBV is made of circular DNA , but it is unusual because the DNA is not fully double

@-@ stranded . One end of the full length strand is linked to the viral DNA polymerase . The genome is 3020 ? 3320 nucleotides long (for the full @-@ length strand) and 1700 ? 2800 nucleotides long (for the short length @-@ strand) . The negative @-@ sense (non @-@ coding) is complementary to the viral mRNA . The viral DNA is found in the nucleus soon after infection of the cell . The partially double @-@ stranded DNA is rendered fully double @-@ stranded by completion of the (+) sense strand and removal of a protein molecule from the (?) sense strand and a short sequence of RNA from the (+) sense strand . Non @-@ coding bases are removed from the ends of the (?) sense strand and the ends are rejoined . There are four known genes encoded by the genome , called C , X , P , and S. The core protein is coded for by gene C (HBcAg) , and its start codon is preceded by an upstream in @-@ frame AUG start codon from which the pre @-@ core protein is produced . HBeAg is produced by proteolytic processing of the pre @-@ core protein . In some rare strains of the virus known as Hepatitis B virus precore mutants , no HBeAg is present . The DNA polymerase is encoded by gene P. Gene S is the gene that codes for the surface antigen (HBsAg) . The HBsAg gene is one long open reading frame but contains three in frame " start " (ATG) codons that divide the gene into three sections , pre @-@ S1 , pre @-@ S2 , and S. Because of the multiple start codons , polypeptides of three different sizes called large (the order from surface to the inside : pre @-@ S1 , pre @-@ S2 , and S) , middle (pre @-@ S2 , S) , and small (S) are produced . The function of the protein coded for by gene X is not fully understood but it is associated with the development of liver cancer . It stimulates genes that promote cell growth and inactivates growth regulating molecules .

= = = = Pathogenesis = = = =

The life cycle of hepatitis B virus is complex . Hepatitis B is one of a few known pararetroviruses : non @-@ retroviruses that still use reverse transcription in their replication process . The virus gains entry into the cell by binding to NTCP on the surface and being endocytosed . Because the virus multiplies via RNA made by a host enzyme , the viral genomic DNA has to be transferred to the cell nucleus by host proteins called chaperones . The partially double stranded viral DNA is then made fully double stranded by viral polymerase and transformed into covalently closed circular DNA (cccDNA) . This cccDNA serves as a template for transcription of four viral mRNAs by host RNA polymerase . The largest mRNA , (which is longer than the viral genome) , is used to make the new copies of the genome and to make the capsid core protein and the viral DNA polymerase . These four viral transcripts undergo additional processing and go on to form progeny virions that are released from the cell or returned to the nucleus and re @-@ cycled to produce even more copies . The long mRNA is then transported back to the cytoplasm where the virion P protein (the DNA polymerase) synthesizes DNA via its reverse transcriptase activity .

= = = = Serotypes and genotypes = = = =

The virus is divided into four major serotypes (adr , adw , ayr , ayw) based on antigenic epitopes presented on its envelope proteins , and into eight genotypes (A ? H) according to overall nucleotide sequence variation of the genome . The genotypes have a distinct geographical distribution and are used in tracing the evolution and transmission of the virus . Differences between genotypes affect the disease severity , course and likelihood of complications , and response to treatment and possibly vaccination .

Genotypes differ by at least 8 % of their sequence and were first reported in 1988 when six were initially described (A ? F) . Two further types have since been described (G and H) . Most genotypes are now divided into subgenotypes with distinct properties .

= = Mechanisms = =

Hepatitis B virus primarily interferes with the functions of the liver by replicating in hepatocytes . A functional receptor is NTCP . There is evidence that the receptor in the closely related duck hepatitis

B virus is carboxypeptidase D. The virions bind to the host cell via the preS domain of the viral surface antigen and are subsequently internalized by endocytosis . HBV @-@ preS @-@ specific receptors are expressed primarily on hepatocytes ; however , viral DNA and proteins have also been detected in extrahepatic sites , suggesting that cellular receptors for HBV may also exist on extrahepatic cells .

During HBV infection , the host immune response causes both hepatocellular damage and viral clearance . Although the innate immune response does not play a significant role in these processes , the adaptive immune response , in particular virus @-@ specific cytotoxic T lymphocytes (CTLs) , contributes to most of the liver injury associated with HBV infection . CTLs eliminate HBV infection by killing infected cells and producing antiviral cytokines , which are then used to purge HBV from viable hepatocytes . Although liver damage is initiated and mediated by the CTLs , antigen @-@ nonspecific inflammatory cells can worsen CTL @-@ induced immunopathology , and platelets activated at the site of infection may facilitate the accumulation of CTLs in the liver .

= = Diagnosis = =

The tests , called assays , for detection of hepatitis B virus infection involve serum or blood tests that detect either viral antigens (proteins produced by the virus) or antibodies produced by the host . Interpretation of these assays is complex .

The hepatitis B surface antigen (HBsAg) is most frequently used to screen for the presence of this infection . It is the first detectable viral antigen to appear during infection . However , early in an infection , this antigen may not be present and it may be undetectable later in the infection as it is being cleared by the host . The infectious virion contains an inner " core particle " enclosing viral genome . The icosahedral core particle is made of 180 or 240 copies of core protein , alternatively known as hepatitis B core antigen , or HBcAg . During this ' window ' in which the host remains infected but is successfully clearing the virus , IgM antibodies specific to the hepatitis B core antigen (anti @-@ HBc IgM) may be the only serological evidence of disease . Therefore , most hepatitis B diagnostic panels contain HBsAg and total anti @-@ HBc (both IgM and IgG) .

Shortly after the appearance of the HBsAg , another antigen called hepatitis B e antigen (HBeAg) will appear . Traditionally , the presence of HBeAg in a host 's serum is associated with much higher rates of viral replication and enhanced infectivity ; however , variants of the hepatitis B virus do not produce the ' e ' antigen , so this rule does not always hold true . During the natural course of an infection , the HBeAg may be cleared , and antibodies to the ' e ' antigen (anti @-@ HBe) will arise immediately afterwards . This conversion is usually associated with a dramatic decline in viral replication .

If the host is able to clear the infection , eventually the HBsAg will become undetectable and will be followed by IgG antibodies to the hepatitis B surface antigen and core antigen (anti @-@ HBs and anti HBc IgG) . The time between the removal of the HBsAg and the appearance of anti @-@ HBs is called the window period . A person negative for HBsAg but positive for anti @-@ HBs either has cleared an infection or has been vaccinated previously .

Individuals who remain HBsAg positive for at least six months are considered to be hepatitis B carriers . Carriers of the virus may have chronic hepatitis B , which would be reflected by elevated serum alanine aminotransferase (ALT) levels and inflammation of the liver , if they are in the immune clearance phase of chronic infection . Carriers who have seroconverted to HBeAg negative status , in particular those who acquired the infection as adults , have very little viral multiplication and hence may be at little risk of long @-@ term complications or of transmitting infection to others .

PCR tests have been developed to detect and measure the amount of HBV DNA , called the viral load , in clinical specimens . These tests are used to assess a person 's infection status and to monitor treatment . Individuals with high viral loads , characteristically have ground glass hepatocytes on biopsy .

= = Prevention = =

Vaccines for the prevention of hepatitis B have been routinely recommended for infants since 1991 in the United States . Most vaccines are given in three doses over a course of months . A protective response to the vaccine is defined as an anti @-@ HBs antibody concentration of at least 10 mIU / ml in the recipient 's serum . The vaccine is more effective in children and 95 percent of those vaccinated have protective levels of antibody . This drops to around 90 % at 40 years of age and to around 75 percent in those over 60 years . The protection afforded by vaccination is long lasting even after antibody levels fall below 10 mIU / ml . Vaccination at birth is recommended for all infants of HBV infected mothers . A combination of hepatitis B immune globulin and an accelerated course of HBV vaccine prevents HBV transmission around the time of birth in 86 % to 99 % of cases .

All those with a risk of exposure to body fluids such as blood should be vaccinated , if not already . Testing to verify effective immunization is recommended and further doses of vaccine are given to those who are not sufficiently immunized .

In assisted reproductive technology , sperm washing is not necessary for males with hepatitis B to prevent transmission , unless the female partner has not been effectively vaccinated . In females with hepatitis B , the risk of transmission from mother to child with IVF is no different from the risk in spontaneous conception .

Those at high risk of infection should be tested as there is effective treatment for those who have the disease . Groups that screening is recommended for include those who have not been vaccinated and one of the following : people from areas of the world where hepatitis B occurs in more than 2 % , those with HIV , intravenous drug users , men who have sex with men , and those who live with someone with hepatitis B.

= = = Duration of vaccination = = =

In 10- to 22 @-@ year follow @-@ up studies there were no cases of hepatitis B among those with a normal immune system who were vaccinated . Only rare chronic infections have been documented .

= = Treatment = =

Acute hepatitis B infection does not usually require treatment and most adults clear the infection spontaneously . Early antiviral treatment may be required in fewer than 1 % of people , whose infection takes a very aggressive course (fulminant hepatitis) or who are immunocompromised . On the other hand , treatment of chronic infection may be necessary to reduce the risk of cirrhosis and liver cancer . Chronically infected individuals with persistently elevated serum alanine aminotransferase , a marker of liver damage , and HBV DNA levels are candidates for therapy . Treatment lasts from six months to a year , depending on medication and genotype .

Although none of the available drugs can clear the infection , they can stop the virus from replicating , thus minimizing liver damage . As of 2008 , there are seven medications licensed for treatment of hepatitis B infection in the United States . These include antiviral drugs lamivudine (Epivir) , adefovir (Hepsera) , tenofovir (Viread) , telbivudine (Tyzeka) and entecavir (Baraclude) , and the two immune system modulators interferon alpha @-@ 2a and PEGylated interferon alpha @-@ 2a (Pegasys) . The World Health Organization recommended a combination of tenofovir and entecavir as first line agents . Those with current cirrhosis are in most need of treatment .

The use of interferon , which requires injections daily or thrice weekly , has been supplanted by long @-@ acting PEGylated interferon , which is injected only once weekly . However , some individuals are much more likely to respond than others , and this might be because of the genotype of the infecting virus or the person 's heredity . The treatment reduces viral replication in the liver , thereby reducing the viral load (the amount of virus particles as measured in the blood) . Response to treatment differs between the genotypes . Interferon treatment may produce an e antigen seroconversion rate of 37 % in genotype A but only a 6 % seroconversion in type D. Genotype B has similar seroconversion rates to type A while type C seroconverts only in 15 % of cases .

Sustained e antigen loss after treatment is ~ 45 % in types A and B but only 25 ? 30 % in types C and D.

= = Prognosis = =

Hepatitis B virus infection may be either acute (self @-@ limiting) or chronic (long @-@ standing) . Persons with self @-@ limiting infection clear the infection spontaneously within weeks to months .

Children are less likely than adults to clear the infection . More than 95 % of people who become infected as adults or older children will stage a full recovery and develop protective immunity to the virus . However , this drops to 30 % for younger children , and only 5 % of newborns that acquire the infection from their mother at birth will clear the infection . This population has a 40 % lifetime risk of death from cirrhosis or hepatocellular carcinoma . Of those infected between the age of one to six , 70 % will clear the infection .

Hepatitis D (HDV) can occur only with a concomitant hepatitis B infection , because HDV uses the HBV surface antigen to form a capsid . Co @-@ infection with hepatitis D increases the risk of liver cirrhosis and liver cancer . Polyarteritis nodosa is more common in people with hepatitis B infection .

= = = Cirrhosis = = =

A number of different tests are available to determine the degree of cirrhosis present . Transient elastography (FibroScan) is the test of choice , but it is expensive . Aspartate aminotransferase to platelet ratio index may be used when cost is an issue .

= = = Reactivation = = =

Hepatitis B virus DNA persists in the body after infection , and in some people the disease recurs . Although rare , reactivation is seen most often following alcohol or drug use , or in people with impaired immunity . HBV goes through cycles of replication and non @-@ replication . Approximately 50 % of overt carriers experience acute reactivation . Males with baseline ALT of 200 UL / L are three times more likely to develop a reactivation than people with lower levels . Although reactivation can occur spontaneously , people who undergo chemotherapy have a higher risk . Immunosuppressive drugs favor increased HBV replication while inhibiting cytotoxic T cell function in the liver . The risk of reactivation varies depending on the serological profile ; those with detectable HBsAg in their blood are at the greatest risk , but those with only antibodies to the core antigen are also at risk . The presence of antibodies to the surface antigen , which are considered to be a marker of immunity , does not preclude reactivation . Treatment with prophylactic antiviral drugs can prevent the serious morbidity associated with HBV disease reactivation .

= = Epidemiology = =

In 2004 , an estimated 350 million individuals were infected worldwide . National and regional prevalence ranges from over 10 % in Asia to under 0 @.@ 5 % in the United States and northern Europe .

Routes of infection include vertical transmission (such as through childbirth) , early life horizontal transmission (bites , lesions , and sanitary habits) , and adult horizontal transmission (sexual contact , intravenous drug use) .

The primary method of transmission reflects the prevalence of chronic HBV infection in a given area . In low prevalence areas such as the continental United States and Western Europe , injection drug abuse and unprotected sex are the primary methods , although other factors may also be important . In moderate prevalence areas , which include Eastern Europe , Russia , and Japan , where 2 ? 7 % of the population is chronically infected , the disease is predominantly spread among children . In

high @-@ prevalence areas such as China and South East Asia , transmission during childbirth is most common , although in other areas of high endemicity such as Africa , transmission during childhood is a significant factor . The prevalence of chronic HBV infection in areas of high endemicity is at least 8 % with 10 ? 15 % prevalence in Africa / Far East . As of 2010 , China has 120 million infected people , followed by India and Indonesia with 40 million and 12 million , respectively . According to World Health Organization (WHO) , an estimated 600 @,@ 000 people die every year related to the infection .

In the United States about 19 @,@ 000 new cases occurred in 2011 down nearly 90 % from 1990 .

= = History = =

The earliest record of an epidemic caused by hepatitis B virus was made by Lurman in 1885 . An outbreak of smallpox occurred in Bremen in 1883 and 1 @,@ 289 shipyard employees were vaccinated with lymph from other people . After several weeks , and up to eight months later , 191 of the vaccinated workers became ill with jaundice and were diagnosed as suffering from serum hepatitis . Other employees who had been inoculated with different batches of lymph remained healthy . Lurman 's paper , now regarded as a classical example of an epidemiological study , proved that contaminated lymph was the source of the outbreak . Later , numerous similar outbreaks were reported following the introduction , in 1909 , of hypodermic needles that were used , and , more importantly , reused , for administering Salvarsan for the treatment of syphilis . The virus was not discovered until 1966 when Baruch Blumberg , then working at the National Institutes of Health (NIH) , discovered the Australia antigen (later known to be hepatitis B surface antigen , or HBsAg) in the blood of Australian aboriginal people . Although a virus had been suspected since the research published by MacCallum in 1947 , D.S. Dane and others discovered the virus particle in 1970 by electron microscopy . By the early 1980s the genome of the virus had been sequenced , and the first vaccines were being tested .

= = Society and culture = =

World Hepatitis Day , observed July 28 , aims to raise global awareness of hepatitis B and hepatitis C and encourage prevention , diagnosis and treatment . It has been led by the World Hepatitis Alliance since 2007 and in May 2010 , it got global endorsement from the World Health Organization .