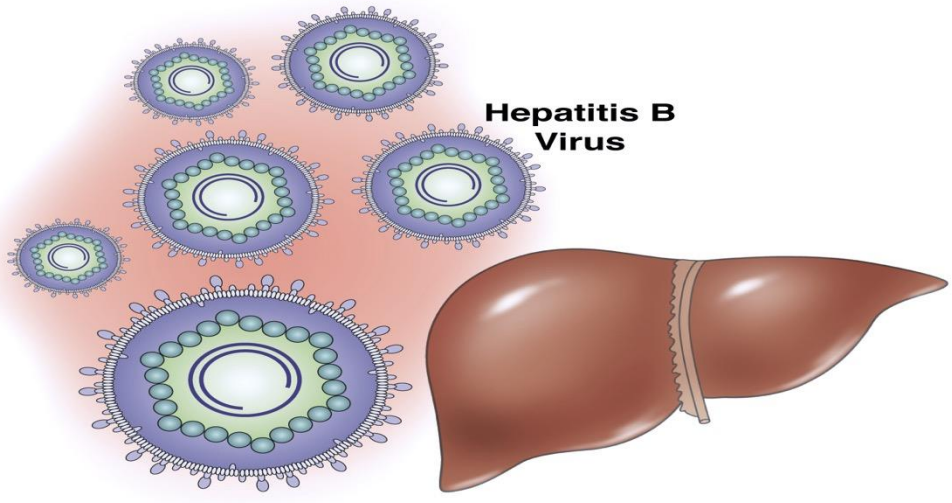
HEPATITIS B VIRUS

(HBV)



Required for Medical Virology Course

By The Students:

Reem Bin Tahnoun 433201038

Abeer Al Khalaf 432925277

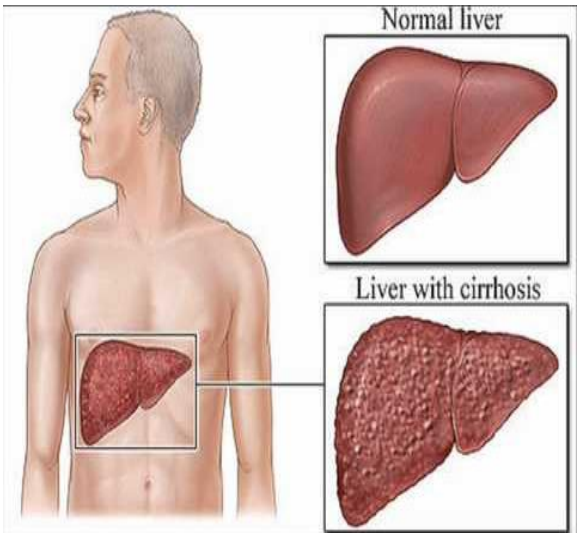
Nourah Al Rshood 433201300

T. Dalia Al Sarar

Table of Contents:

Introduction:

A. History of Disease:



Hepatitis B is an infectious liver disease caused by the hepatitis B virus (HBV). Hepatitis B may cause acute hepatitis or chronic liver disease including primary liver cancer.

The different outcomes of infection (either acute or chronic) are related to the way different individuals respond to infection. For the most part, this is determined by the age of the individual being infected. Perinatal infection – symptoms of acute infection are rare, but 90% of infants develop chronic infection. The lifetime risk of advanced liver disease for infected infants is 20% to 30% Childhood infection – symptoms of acute infection are uncommon, but 30% of children exposed to HBV develop chronic infection. The lifetime risk for children who develop chronic infection is 20% to 30% Adult/adolescent infection – symptoms of acute infection are common, but there is less than a 5% chance of chronic infection. The lifetime risk of advanced liver disease among people with chronic infection is 20 to 30%.

- **Acute**

Acute HBV is more likely to occur in adults – this is mainly due to the ability of adults to produce an active immune response to the presence of HBV. This active response is responsible for acute inflammation in the liver, producing the symptoms of acute infection. Symptoms tend to occur approximately 12 weeks after initial infection and include jaundice, anorexia (loss of appetite), lethargy, nausea, abdominal pain, myalgia (muscle pain) and arthralgia (joint pain). The active immune response is also responsible for helping 'clear' the virus from the body and preventing chronic infection. In babies, the immune system is less able to respond effectively to the presence of virus

in the body. As a result, the active immune response is less likely to occur (younger children are less likely than older children to mount an effective immune response) reducing the chances of an infected baby displaying either the symptoms of acute infection whilst increasing the chances of developing a chronic infection.

- **Chronic**

Individuals with chronic HBV infection are commonly asymptomatic for many years. This is because HBV multiplies in the hepatic (liver) cells causing little obvious damage. The infected hepatic cells are then killed by the body's immune system (over a long period of time), which can lead to cirrhosis (scarring of the liver) and in some cases hepatocellular carcinoma (primary liver cancer). Approximately 25% of people chronically infected with HBV will develop cirrhosis, and one in five people with cirrhosis will then develop hepatocellular carcinoma.

B. Introduction of this virus:

Hepatitis B is transmitted when blood, semen, or another body fluid from a person infected with the Hepatitis B virus enters the body of someone who is not infected. This can happen through sexual contact; sharing needles, syringes, or other drug-injection equipment; or from mother to baby at birth.

The incubation period of HBV ranges from 45 to 160 days (mean, 100 days). Symptoms therefore range widely in severity, from asymptomatic subclinical infection to fulminant fatal disease. An insidious onset of nausea, anorexia, malaise, and fatigue, or flulike symptoms, such as pharyngitis, cough, coryza, photophobia, headache, and myalgias, can precede the onset of jaundice. Fever is uncommon, unlike with hepatitis A infection.

The best way to prevent Hepatitis B is by getting vaccinated.

C. The Distribution of the Disease:

Worldwide. Hepatitis B prevalence is highest in sub-Saharan Africa and East Asia, where between 5–10% of the adult population is chronically infected. High rates of chronic infections are also found in the Amazon and the southern parts of eastern and central Europe. In the Middle East and the Indian subcontinent, an estimated 2–5% of the general population is chronically infected. Less than 1% of the population in Western Europe and North America is chronically infected.

D. Epidemiology:

Liver disease related to hepatitis B remains an important public health concern and a major cause of morbidity and mortality. It also presents a common challenging problem for practicing physicians.

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.

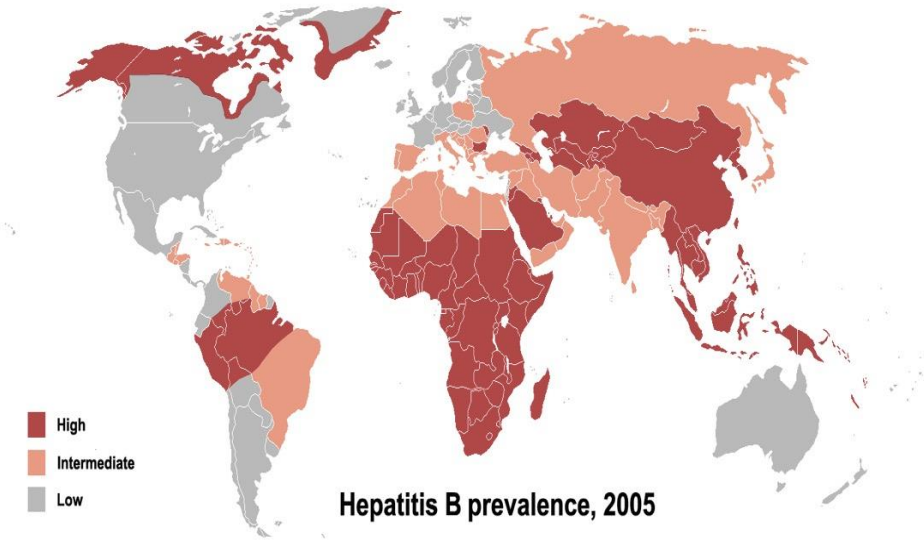
In moderate prevalence areas, which include Eastern Europe, Russia, and Japan, where 2–7% of the population is chronically infected, the disease is predominantly

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.[84] 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.

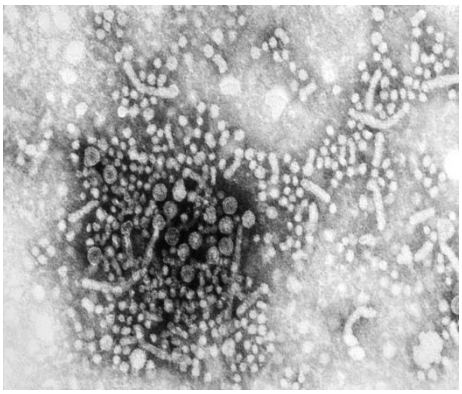
Worldwide, chronic hepatitis B is the tenth leading cause of death.



Hepatitis B prevalence, 2005

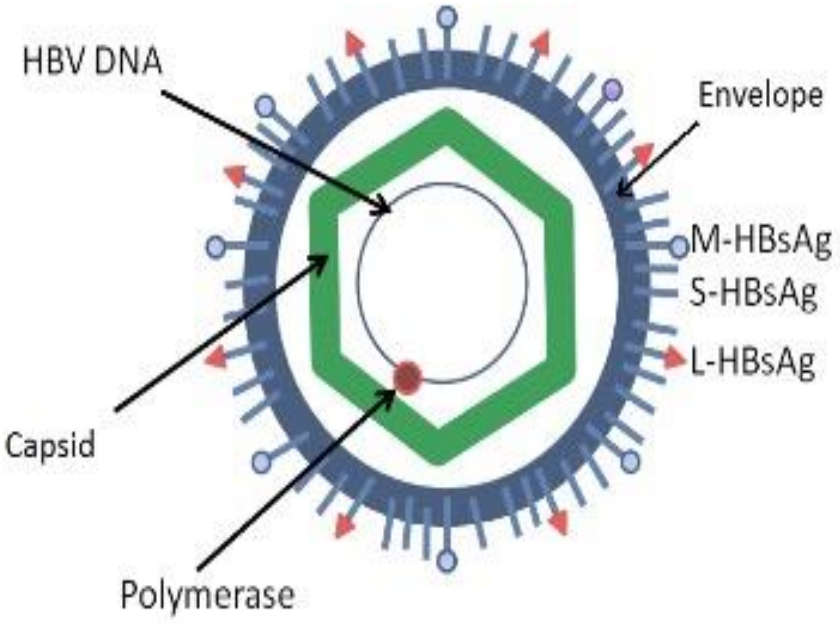
Classification:

Order	Unassigned
Family	*Hepadnaviridae*
Genus	*Orthohepadnavirus*



Structure and Genome:

Shape	Circular or oval in shape.
Size	30 to 42 nm in dimeter
Enveloped or not ?	Enveloped icosahedral virus.
Nucleic acid	HBV is Reverse transcriptase double-stranded DNA virus , (dsDNA-RT virus)



7

Proteins:

A. Structural proteins and their function:

The X gene is conserved among mammalian hepadnaviruses and the X protein, pX, is essential for viral propagation at least in the woodchuck. During the last decade, efforts have centered on elucidating the oncogenic role of pX in hepatitis B virus infection. The accumulating knowledge on pX indicates that it is a multifunctional regulatory protein which modulates many host functions by communicating directly or indirectly with a variety of host targets as is the case for many viral regulatory proteins, such as T antigens, E1A, and human T cell lymphotropic virus tax. pX, which modulates the transcription machinery and/or modulation protein kinase signaling cascades, transactivates many host genes involved in cell proliferation, cytokine networks, acute immune response, and house-keeping functions. Distinct from the transactivation, pX also modulates DNA repair processes by interacting with p53 and/or repair enzymes which may accumulate mutations and sensitize cells to genotoxic stimuli. Several X-interaction host proteins remain to be characterized as targets of pX. The biological roles of pX have been addressed in various systems in addition to the role of pX on viral reproduction. pX may affect cell cycle progress, response to apoptotic stimuli, cell transformation, and carcinogenesis in the presence or absence of additional oncogenic factors. These biological roles of pX have not been described in terms of pX functions and targets and remain subjects of future research using improved experimental systems and technologies. Such efforts will identify important function(s) of pX for hepatocarcinogenesis.

The genomes of six hepatitis B viral (HBV) strains were sequenced from 10 overlapping amplificates obtained by the polymerase chain reaction. Four of the strains,

specifying subtypes ayw4 and adw4q-, represented on the basis of divergency within the S gene two new genomic groups identified by us. The other two strains, encoding adrq- and of Pacific origin, belonged to genomic group C. The relation of these genomes to 21 published human, 1 chimpanzee, and 4 rodent hepadnaviral genomes was analyzed by constructing a phylogenetic dendrogram. Thereby, the segregation of human HBV strains into six genomic groups was confirmed. A consistent grouping of the genomes compared was also obtained in dendrograms based on the P and S genes, although the branching order differed from that based on the entire genomes. Each of the two representatives of genomic groups E and F differed by 8.1 to 13.6% and by 12.8 to 15.5% from the genomes of the other groups and by 1.5 and 3.7% from each other. The two Pacific group C strains differed by 2.7% from each other and by 4.1 to 5.4% from other group C genomes, suggesting that they diverged early from the other group C genomes. The F strains formed the most divergent group of HBV genomes, which may be explained by their representing the original strains of the New World. Within the structural gene products, 17 and 34 amino acids unique for human HBV strains were recorded in the sequenced E and F strains, respectively. Most notable is the Ser81 to Ala81 substitution in an immunodominant region of HBcAg, and the four extra cysteine residues in HBsAg at residues 19, 183, 206, and 220, which might be engaged in additional disulphide bridges. Five residues shared by E and F strains were also unique for human HBV strains. Two of these, Leu127 and Ser140 in HBsAg, were the only substitutions that may explain the w4 reactivity shared by these HBV strains. Interestingly, the Ser140 substitution occurs in an immunodominant loop of the a determinant claimed to be important for the protective immune response to HBV vaccination.

B. Non structural protein:

The cytotoxic T-cell response in chronic hepatitis B virus (HBV) infection has been described as weak and mono- or oligospecific in comparison to the more robust virus-specific T-cell response present in resolved infection. However, chronic hepatitis B is a heterogeneous disease with markedly variable levels of virus replication and liver disease activity. Here we analyzed (both directly ex vivo and after in vitro stimulation) the HBV-specific CD8 T-cell responses against structural and nonstructural HBV proteins longitudinally in patients with different patterns of chronic infections. We found that the profiles of virus-specific CD8+-T-cell responses during chronic infections are highly heterogeneous and influenced more by the level of HBV replication than by the activity of liver disease. An HBV DNA load of <107 copies/ml appears to be the threshold below which circulating multispecific HBV-specific CD8+ T cells are consistently detected. Furthermore, CD8+ T cells with different specificities are differentially regulated during chronic infections. HBV core-specific CD8+ T cells are associated with viral control, while CD8+ T cells specific for envelope and polymerase epitopes can occasionally be found in the setting of high levels (>107 copies) of HBV replication. These findings have implications for the design of immunotherapy for chronic HBV infection.

Transmission:

Hepatitis B is found in blood and in body fluids, including semen and vaginal fluids. Even though studies have shown minute quantities of the virus can be present in saliva, tears and breast milk, they are not considered to be in high enough levels to transmit the virus.

The most common ways hepatitis B is spread include:

- sexual contact
- sharing of injecting equipment
- needlestick injuries in a health care setting
- reuse of unsterilised or inadequately sterilised needles
- child-to-child transmission through household contact such as biting
- sharing personal items such as razors, toothbrushes, or hair and nail clippers

mother-to-baby, though it is to be noted that the Australian vaccination program has significantly reduced this risk through the administration of the vaccine within 12 hours of birth.

Hepatitis B is **NOT** spread by contaminated food or water, and cannot be spread through casual or social contact such as kissing, sneezing or coughing, hugging, or eating food prepared by a person with hepatitis B.

- **Prevention**

To avoid transmission of hepatitis B:

- consider being vaccinated (see below for more details);
- practice safe sex (use a condom)
- wash hands after touching blood or body fluids
- wear disposable gloves if giving someone first aid, or cleaning up blood or body fluids
- avoid sharing toothbrushes, razors, needles, syringes, personal hygiene items and grooming aids or any object that may come into contact with blood or body fluids
- use new and sterile injecting equipment for each injection
- cover all cuts and open sores with a bandaid or bandage
- wipe up any blood spills and then clean the area with household bleach

- throw away personal items such as tissues, menstrual pads, tampons and bandages in a sealed plastic bag.

People who have been exposed to the hepatitis B virus and who have not been vaccinated should receive hepatitis B immunoglobulin (HBIG) within 72 hours of exposure, and a dose of hepatitis B vaccine as soon as possible or within 7 days of the exposure from their general practitioner or local emergency department.

Penetration and the Target Organ:

THE LIVER AS A TARGET FOR HEPADNAVIRUS INFECTION

The liver plays an essential role in energy storage and conversion, blood homeostasis, chemical detoxification, and immunity to microbial infections. Although the liver is composed of many different types of cells, much of the functional activity resides in hepatocytes (which constitute 70% of the liver), bile ductule epithelium, and Kupffer cells (macrophages) (62). Among these, hepatocytes and bile ductule epithelial cells are unique to the liver and are also closely related. In fact, they may originate during embryonic life from a common progenitor (188, 189, 211) and also may be replaced by proliferation and differentiation of a common progenitor cell in response to very acute forms of liver injury (211).

Because hepatocytes are the major cell type in the liver, it might be expected that they would also be the major target of infection by a liver-tropic virus such as HBV. Indeed, this appears to be the case. Hepatocytes are the only confirmed site of replication for all members of this virus family. Bile ductule epithelial cells may also be a target of infection, as may a subset of cells in the pancreas, kidneys, and lymphoid system (16, 74, 77, 98, 111, 122, 151, 160, 170, 187,243). However, the evidence for replication of the orthohepadnaviruses in bile ductules and at extrahepatic sites is in some cases controversial or incomplete, and these sites are not usually considered in

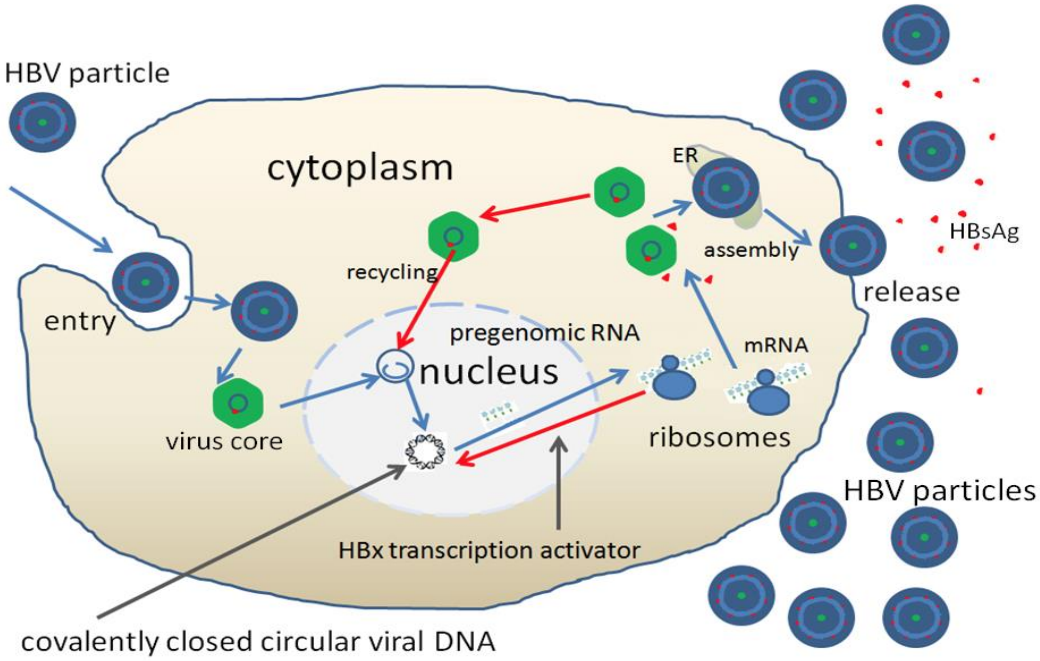
discussions of viral reproduction and pathogenesis. This approach to infections is at least compatible with the notion that many of the extrahepatic symptoms of infection that are not attributed to liver dysfunction are the result of deposition of antibody-antigen complexes. Thus, for the purpose of simplicity, we discuss infection only in the context of hepatic manifestations. The implications of extrahepatic infections have yet to be determined.

The liver itself is usually considered, for convenience, to be divided into small compartments called lobules. This subdivision emphasizes the role of the liver in relation to blood flow. While this view of liver anatomy is somewhat arbitrary, it provides a convenient way of considering liver function, development, regeneration, and pathogenesis. An essentially one-dimensional view of a section of a "classical" lobule is illustrated in Fig.1. In this view, blood enters the lobule through portal veins and hepatic arteries and is distributed by smaller vessels to enter the sinusoidal spaces, created by plates of hepatocytes. The plates are generally one hepatocyte thick in mammals and two hepatocytes thick in birds. Blood passes through these spaces, which are lined by fenestrated endothelial cells and fixed macrophages (Kupffer cells), where the various functional interactions take place. The blood is then collected in central veins and exits the liver. (It should be noted that because of the rather homogeneous nature of liver anatomy, blood from each portal vein and artery will flow to several surrounding central veins; a more thorough discussion of liver structure and function is presented in reference 55. Generally, the distance from a portal vein to a central vein is 20 to 30 hepatocytes. During catabolism of heme produced by red blood cell breakdown in the liver, bile is formed and secreted into bile canaliculi, small channels formed at the junctions of hepatocytes. Bile flows in the opposite direction from blood, passing through a region known as the canal of Hering to enter bile ducts. From there, it flows into larger ducts and is eventually transported to the gallbladder and intestine.

Although hepatocytes are "terminally" differentiated, they retain the capacity for extensive proliferation in response to liver injury. Under normal conditions, hepatocytes may have lifetimes exceeding 6 to 12 months. However, when required, virtually the entire population may enter the cell cycle and divide. Following partial hepatectomy of 70% of the liver, virtually every hepatocyte passes through the cell cycle at least once, and the liver cell mass is restored within a few days (67, 132). In an even more extreme example of liver cell proliferation, Rhim et al. (175) observed, under conditions of very acute liver injury, the replacement of virtually the entire hepatocyte population of the mouse by clonogenic outgrowth of mature hepatocytes. This required an average of at least 12 cycles of cell division.

Hepatocyte replacement may also occur via proliferation of progenitor cells, a situation that appears in the context of long-term liver injury and/or acute injury (e.g., caused by some hepatotoxic drugs) in which hepatocyte proliferation is retarded. These progenitors are thought to be a population of facultative stem cells present in the region of the portal tracts, possibly closely associated with or identical to cells in bile ducts or the canals of Hering (36, 42,54, 56, 212). When induced to proliferate, they may first appear as the so-called oval cells (176) and may then differentiate to form hepatocytes.

Replication Cycle:



The life cycle of hepatitis B virus is complex. Hepatitis B is one of a few known non-retroviral viruses which use reverse transcription as a part of its replication process.

- **Attachment**

The virus gains entry into the cell by binding to a receptor on the surface of the cell and enters it by clathrin-dependent endocytosis. The cell surface receptor has been identified as the Sodium/Bile acid cotransporting pepetide SLC10A1 (also named NTCP).

- **Penetration**

The virus membrane then fuses with the host cell's membrane releasing the DNA and core proteins into the cytoplasm.An internal ribosome entry site within the 5 nontranslated segment of the genome mediates cap-independent translation of the viral polyprotein.

- **Uncoating**

Because the virus multiplies via RNA made by a host enzyme, the viral genomic DNA has to be transferred to the cell nucleus. It is thought the capsid is transported on the microtubules to the nuclear pore. The core proteins dissociate from the partially double stranded viral DNA is then made fully double stranded and transformed into covalently closed circular DNA (cccDNA) that serves as a template for transcription of four viral mRNAs.

- **Replication**

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.

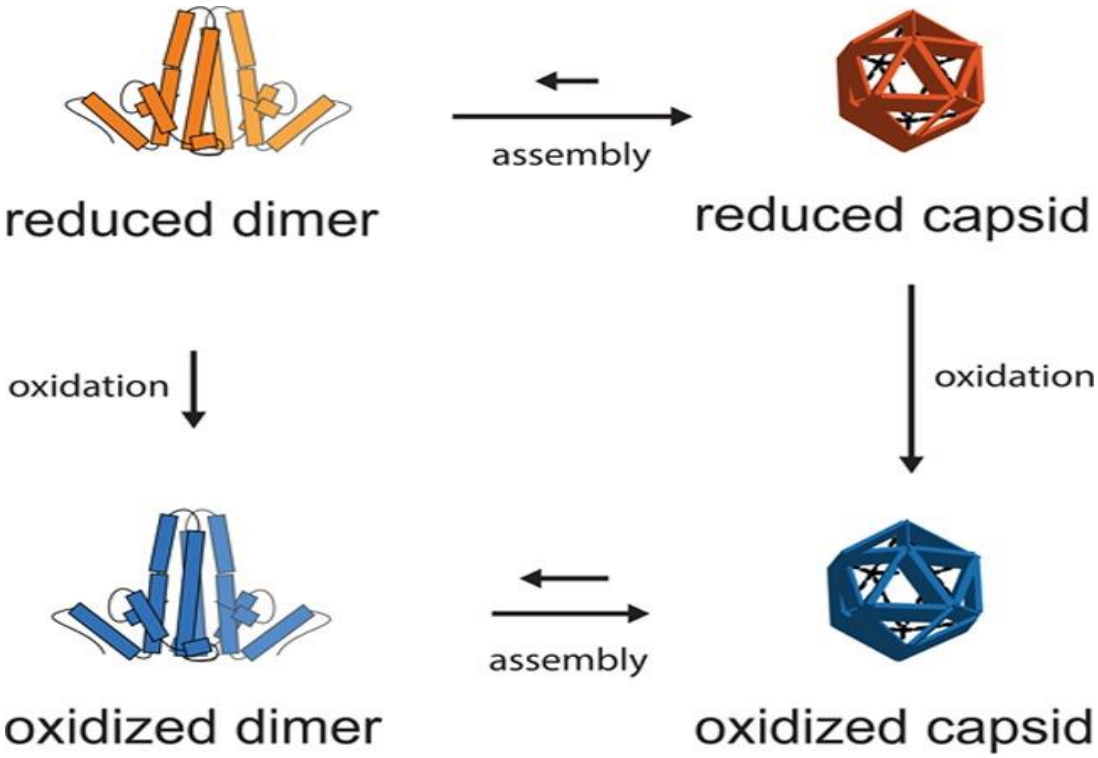
- **Assembly**

These four viral transcripts undergo additional processing and go on to form progeny virions which are released from the cell or returned to the nucleus and re-cycled to produce even more copies.

- **Release**

The long mRNA is then transported back to the cytoplasm where the virion P protein synthesizes DNA via its reverse transcriptase activity.

Assembly and Egression:



During the hepatitis B virus (HBV) life cycle, capsid assembly and disassembly must ensure correct packaging and release of the viral genome. Here we show that changes in the dynamics of the core protein play an important role in regulating these processes. The HBV capsid assembles from 120 copies of the core protein homodimer. Each monomer contains a conserved cysteine at position 61 that can form an intradimer disulfide that we use as a marker for dimer conformational states. We show that dimers in the context of capsids form intradimer disulfides relatively rapidly. Surprisingly, compared to reduced dimers, fully oxidized dimers assembled slower and into capsids that were morphologically similar but less stable. We hypothesize that oxidized protein adopts a geometry (or constellation of geometries) that is unfavorable for capsid assembly, resulting in weaker dimer–dimer interactions as well as slower assembly kinetics. Our results suggest that structural flexibility at the core protein intradimer

interface is essential for regulating capsid assembly and stability. We further suggest that capsid destabilization by the C61–C61 disulfide has a regulatory function to support capsid disassembly and release of the viral genome.

Icosahedral virus capsid assembly is a highly regulated, efficient process in which tens to hundreds of capsid proteins form a stable virus shell. During the virus life cycle, capsid assembly has to be regulated to ensure correct packaging and release of the viral genome. Newly formed capsids must be stable to withstand the extracellular environment. Capsids also must be unstable enough to allow disassembly, to release the viral genome.

One mechanism regulating virus capsid assembly is allosteric activation, described as dynamic or conformational changes that switch the capsid protein from assembly inactive to assembly active states. Allosteric changes during assembly help to package the right nucleic acid to define the nucleation step and contribute to an induced fit mechanism for elongation. Nucleation and induced fit both minimize the accumulation of intermediates.

Allosteric regulation, mediated by binding of nucleic acid to the capsid protein, has been observed in retroviruses and bacteriophage MS2. Also, extensive studies of the hepatitis B virus (HBV) capsid protein indicate allosteric changes during assembly, independent of nucleic acid binding. Assembly studies show that zinc ions induce a conformational change to the HBV capsid protein dimer that alters its assembly behavior. Additionally, X-ray crystallography revealed structural differences between free HBV dimers and dimers in capsids.

The HBV capsid is formed from 120 core protein homodimers that are arranged with T = 4 icosahedral symmetry. A small portion of the HBV capsids have T = 3 icosahedral symmetry and consist of 90 homodimers. The full-length core protein has 183 amino acids and is comprised of an assembly domain (amino acids 1–149) and a

nucleic acid-binding domain (amino acids 150–183). The assembly domain, termed Cp149 in this paper, can be expressed in Escherichia coli and assembles spontaneously in response to an increase in ionic strength. Cp149 thereby forms particles that are morphologically indistinguishable from capsids isolated from cell cultures.

In vitro capsid assembly of HBV has been well-characterized. Simulations and light scattering experiments have shown that the assembly of large populations of particles displays sigmoidal kinetics.

Assembly for each capsid starts with nucleation that is followed by elongation and growth involving the addition of free dimer subunits. Because observations of in vitro assembly reactions typically are based on very large ensembles of molecules, interpretation of assembly kinetics requires particular care. For example, the initial lag phase during assembly kinetics is the time to establish a steady stream of intermediates.

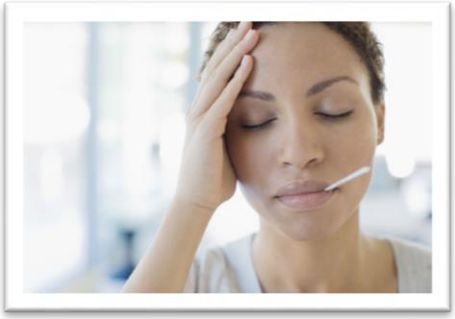
HBV capsid assembly is defined by multiple weak interdimer contact energies [approximately 3–5 kcal/mol (5–8 kT)]. However, a T = 4 HBV capsid has 240 interdimer contacts. In comparison, association energies found in antibody–protein interactions were approximately 11–15 kcal/mol or 15–25 kT.

In this study, we investigated how changes at the intradimer interface, the monomer–monomer contact region, propagate to the interdimer interface to influence HBV core protein assembly and capsid stability. We utilized a pair of cysteine residues located at position 61 that can form an intradimer disulfide bond. Cysteine 61 is conserved throughout all mammalian HBV core proteins .The C61–C61 disulfide has been shown to form within HBV particles assembled from full-length core protein expressed in E. coli. However, recent reports found no disulfide in freshly purified RNA-filled capsids, indicating oxidation of capsids formed by full-length protein might be slower than that in empty capsids formed by Cp149, and there are no data for mature DNA-filled capsids. We observed that formation of the C61–C61 disulfide bond alters

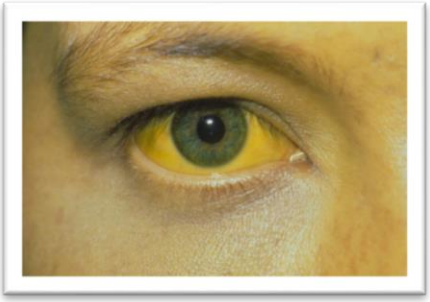
capsid assembly and stability. Free dimers oxidized slowly compared to dimer within capsid, which led us to hypothesize that the oxidized form would favor capsid assembly. However, oxidized Cp149 dimers assemble slowly to form capsids that are less stable than reduced capsids. We thereby show that changes at the intradimer interface are an important regulator of assembly. However, our results also suggest that disulfide bond formation during the HBV life cycle may promote the disassembly required to release the viral genetic material.

Symptoms:

Most people who have an acute hepatitis B infection don't have symptoms. But if you do have symptoms, they may **include:**



- Extreme tiredness (fatigue)
- Mild fever
- Headache
- Loss of appetite , nausea, and vomiting.
- Constant discomfort on the right side of the belly under the rib cage. (That's where the liver is located)
- Tan-colored bowel movements (stools)
- Dark urine.
- Jaundice. This means that the skin and whites of the eyes look yellow. Jaundice is a major sign of liver damage. It usually appears after other symptoms have started to go away.



Most people who have chronic infection have no symptoms.

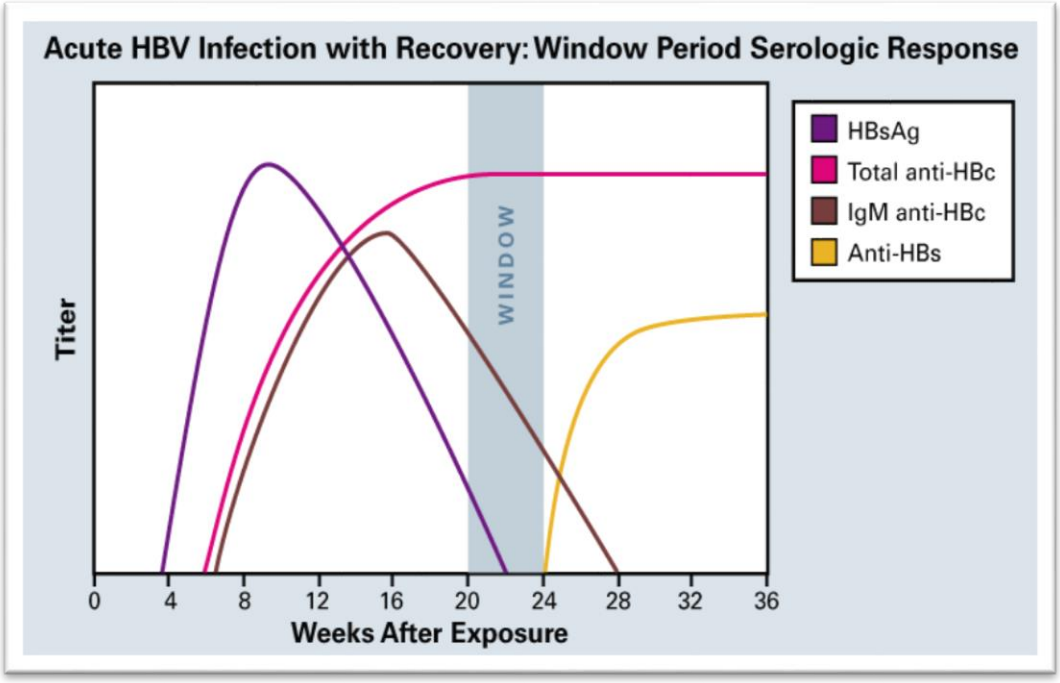
You may get infected without knowing it. You may not find out that you have an infection until you have a routine blood test or donate blood. Finding out that a family member or someone you live with is infected also may cause you to be tested. Some people never know they have hepatitis B until a doctor finds that they have cirrhosis or liver cancer.

Diagnosis:

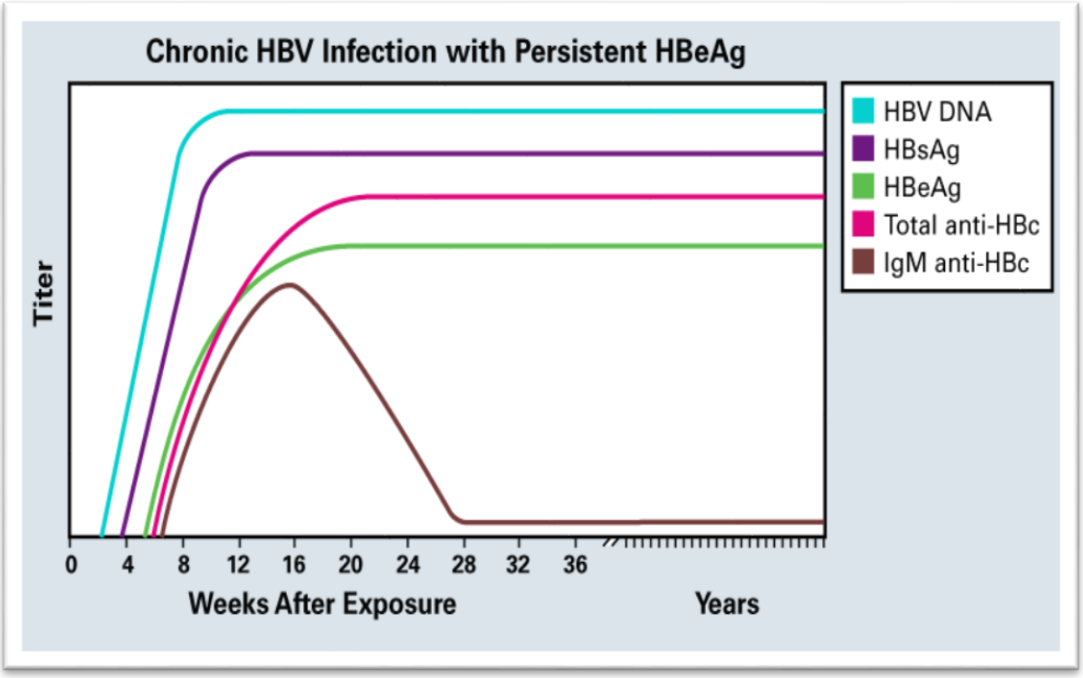
It is not possible, on clinical grounds, to differentiate hepatitis B from hepatitis caused by other viral agents and, hence, laboratory confirmation of the diagnosis is essential. A number of blood tests are available to diagnose and monitor people with hepatitis B. They can be used to distinguish acute and chronic infections.

Laboratory diagnosis of hepatitis B infection focuses on the detection of the hepatitis B surface antigen HBsAg. WHO recommends that all blood donations are tested for hepatitis B to ensure blood safety and avoid accidental transmission to people who receive blood products.

Acute HBV infection is characterized by the presence of HBsAg and immunoglobulin M (IgM) antibody to the core antigen, HBcAg. During the initial phase of infection, patients are also seropositive for hepatitis B e antigen (HBeAg). HBeAg is usually a marker of high levels of replication of the virus. The presence of HBeAg indicates that the blood and body fluids of the infected individual are highly contagious.

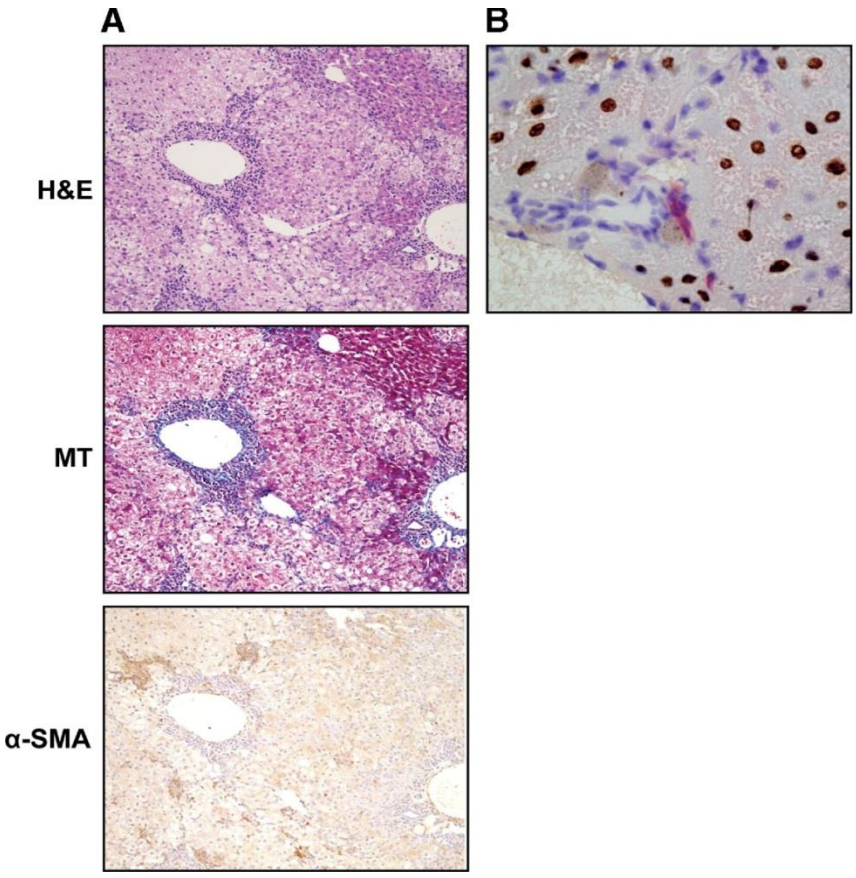


Chronic infection is characterized by the persistence of HBsAg for at least 6 months (with or without concurrent HBeAg). Persistence of HBsAg is the principal marker of risk for developing chronic liver disease and liver cancer (hepatocellular carcinoma) later in life.



Cytopathic Effect:

Little is known about the direct cytopathic effect of hepatitis B virus (HBV) and its association with particular viral genotype or genetic mutation. But there is a study shows that by using a humanized in vivo model, different HBV genotypes and even particular mutations resulted in different virologic and histopathologic outcomes of infection, indicating that particular genetic variants of HBV may be directly cytopathic in immunosuppressive conditions.



(Confirmation of liver fibrosis by immunostaining using anti–α-SMA antibody. (A) Liver sections stained with H&E, MT, or immunostaining using anti–α-SMA antibody (as described in the Materials and Methods section). (B) Nuclei stained brown with the antibodies indicate human origin, and α-SMA is stained in red, located in the cytoplasm without a stained nucleus. Shown are representative staining of images expressing fibrosis. Original magnification, 200.×)

23

Control the Virus and Prevention:

WHO aims at controlling HBV worldwide to decrease the incidence of HBV-related chronic liver disease, cirrhosis, and hepatocellular carcinoma. by integrating HB vaccination into routine infant (and possibly adolescent) immunization programmes.

Persons infected with HBV during infancy or early childhood are more likely to become infected chronically and to develop life-shortening chronic liver disease such as cirrhosis or even liver cancer than adults. This is one important reason why emphasis should be placed upon preventing HBV among the youngest age groups.

In 1991, the Global Advisory Group of EPI (Expanded Programme on Immunization) set 1997 as the target for integrating the hepatitis B vaccination into national immunization programmes worldwide. The group recommended strategies for implementation and delivery that vary according to epidemiology: advocating integration of the vaccine into immunization programmes by 1995 in countries with a HBV carrier prevalence of 8% or higher, and setting 1997 as the target date for all other countries. WHO endorsed the recommendation in May 1992, and the World Health Assembly added a disease reduction target for hepatitis B in 1994, calling for an 80% decrease in new HBV child carriers by 2001 .

Commitment of public health resources to eliminate the spread of HBV requires recognition of the importance of hepatitis B, persistent efforts to ensure that populations are protected, and patience to achieve the goals of disease reduction.

Treatment :

There is usually no specific treatment for acute (short-term) hepatitis B. Unless symptoms are particularly severe, the patient should be able to manage them at home.

The patient can take over-the-counter painkillers such as paracetamol and may

be prescribed codeine if the pain is more severe. Nausea (feeling sick) can often be controlled with a medication called metoclopramide.

If diagnosed as having a hepatitis B infection, regular blood tests and physical check-ups will be advised .

Once symptoms get better, further testing will be needed to check that the patient is free of the virus and have not developed chronic hepatitis B.

A. Vaccines:

In 1981, the Food and Drug Administration approved the first vaccine for hepatitis B, which was plasma-derived (i.e. made from blood products). This vaccine was discontinued in 1990 and is no longer available in the U.S.

The currently used hepatitis B vaccines are made synthetically (i.e. they do not contain blood products) and have been available in the U.S. since 1986.

- Vaccine Schedule:

Three doses are generally required to complete the hepatitis B vaccine series, although there is an accelerated two-dose series for adolescents.

- First Injection - At any given time
- Second Injection - At least one month after the first dose
- Third Injection - Six months after the first dose

-Approved Hepatitis B Vaccines:

There are currently two commercial vaccines used to prevent hepatitis B infection among infants, children and adults in the United States. They are both manufactured using recombinant technology and neither contains blood products. You cannot get hepatitis B from these vaccines.

Engerix-B, Recombivax HB, There is also a combination vaccine for hepatitis A and B available for adults: TwinRix .

This safe and effective vaccine is recommended for all infants at birth and for children up to 18 years. Adults, especially those who fall into a high-risk group, should also seriously consider getting the hepatitis B vaccine.

B. Medication:

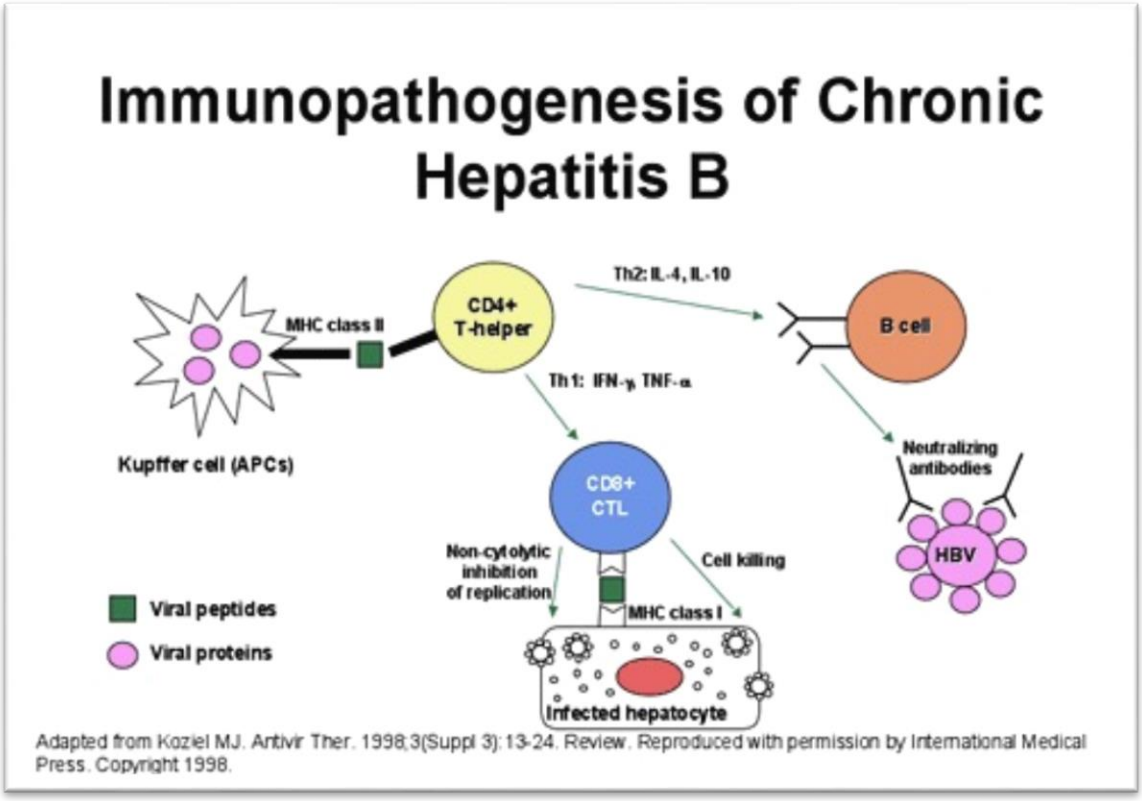
If diagnosed with chronic hepatitis B infection, the treatment to reduce the risk of liver disease and prevent from passing the infection to others. Treatments **include:**

- **Antiviral medications.** Several antiviral medications — including lamivudine (Epivir), adefovir (Hepsera), telbivudine (Tyzeka) and entecavir (Baraclude) — can help fight the virus and slow its ability to damage the liver.
- **Interferon alfa-2b (Intron A).** This synthetic version of a substance produced by the body to fight infection is used mainly for young people with hepatitis B who don't want to undergo long-term treatment or who might want to get pregnant within a few years. It's given by injection. Side effects may include depression, difficulty breathing and chest tightness.
- **Liver transplant.** If the liver has been severely damaged, a liver transplant may be an option. During a liver transplant, the surgeon removes damaged liver and replaces it with a healthy liver. Most transplanted livers come from deceased donors, though a small number come from living donors who donate a portion of their livers.

Other drugs to treat hepatitis B are being developed.

Host Immune Defense:

HBV is not cytotoxic but destroys liver cells indirectly by provoking an immunologic response Kupffer cells endocytose viral antigens and present them bound to MHC class II molecules to T-helper cells. These CD4+ cells recognize the antigens and release cytokines that direct B-cell and cytolytic T-cell (CTL) activity. Stimulated B cells produce specific antibodies, including neutralizing antibodies. CTLs recognize viral peptides bound to MHC class I molecules on hepatocyte surfaces, leading to destruction of infected hepatocytes. In persons who fail to mount a sufficiently vigorous immune response to HBV during acute infection, chronic infection develops, and the persistent, ineffective immune response results in progressive liver damage and fibrosis.



Genetics (gene mutaition):

Naturally occurring envelope, precore, core, and polymerase variants have been described.* ** Envelope antigenic variants may have a selective advantage over wild type under immune selection pressure, as observed in some cases after hepatitis B IG (HBIG) treatment or HBV vaccination. An epidemiological shift has not been observed yet.

A number of precore mutations preventing HBeAg synthesis have been identified inHBeAg negative carriers. The most frequent variant has a G to A point mutation atnucleotide 83 (mutant HBV83, nucleotide 1896 of the genome, amino acid 144) in theprecore region, introducing a stop codon at codon 28.** The HBV83 mutant is predominantly found in Mediterranean and Asian countries but is uncommon in North America and Northern Europe. Precore mutants are found in patients with fulminanthepatitis or chronic active hepatitis, but also in asymptomatic carriers.*

HBV core gene mutations have been reported in patients from Japan, Hong Kong,United States, and Italy. Most of the mutations are concentrated in the middle-third of the core gene, but although many of these mutations are located in regions thatharbor B and T cell epitopes, they have not been proven to result in loss of immune recognition.

In rare patients where the function of the polymerase gene is impaired, additional compensatory mutations were found that minimized the impact of the impaired function of the polymerase.

HBV is far more heterogeneous than is generally thought. The HBV genome seems not to be characterized by a single representative genomic molecule, but by a pool of genomes which differ both in structure and function.

The public health importance of mutant hepatitis B viruses is currently under

debate. Further studies and a strict surveillance to detect the emergence of these virusesare crucial for a correct evaluation of the effectiveness of current immunization strategies.***

Recent discoveries:

Differing Prospects for the Future of Using Gene Therapy to Treat Infections with Hepatitis B Virus and Hepatitis C Virus

Published on September 28, 2015

http://www.ncbi.nlm.nih.gov/pubmed/26463095

References:

- Centers for Disease Control and Prevention. Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the immunization practices advisory committee (ACIP). Morbidity and Mortality Weekly Report, 1991, 40:1-19,
- Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
- Gitlin N. Hepatitis B: diagnosis, prevention, and treatment. Clinical Chemistry, 1997, 43:1500-1506.
- Hollinger FB, Liang TJ. Hepatitis B Virus. In: Knipe DM et al., eds. Fields Virology, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2001:2971-3036.
- Mahoney FJ, Kane M. Hepatitis B vaccine. In: Plotkin SA and Orenstein WA, eds. Vaccines, 3rd ed. Philadelphia, W.B. Saunders Company, 1999:158-182
- Research Center for Hepatitis & Immunology, Kohnodai Hospital, International Medical Center of Japan, Chiba, Japan
- Van Damme P, Kane M, and Meheus A. Integration of hepatitis B vaccination into national immunization programmes. British Medical Journal, 1997, 314:1033-1037.

- Zuckerman AJ. Hepatitis Viruses. In: Baron S, eds. Medical Microbiology, 4th ed. The University of Texas Medical Branch at Galveston, 1996:849-863.
- Zuckerman AJ. Effect of hepatitis B virus mutants on efficacy of vaccination. Lancet, 2000, 355:1382-1384.
- https://en.wikipedia.org/wiki/Hepatitis_B_virus
- https://en.wikipedia.org/wiki/Hepatitis_B#Epidemiology
- http://jvi.asm.org/content/78/11/5707.short
- http://mmbr.asm.org/content/64/1/51.full
- https://microbewiki.kenyon.edu/index.php/Hepatitis_B_virus
- http://viralzone.expasy.org/all_by_species/101.html
- http://www.cdc.gov/hepatitis/hbv/
- http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hepatology/hepatitis-b/
- http://www.hepatitisaustralia.com/hepatitis-b-facts/transmission
- http://www.hepb.org/hepb/vaccine_information.htm
- http://www.karger.com/Article/Abstract/24969
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4151697/
- http://www.nhs.uk/Conditions/Hepatitis-B/Pages/Treatment.aspx
- http://www.sciencedirect.com/science/article/pii/S0042682284710609
- http://www.webmd.com/hepatitis/hepb-guide/hepatitis-b-symptoms
- http://www.who.int/mediacentre/factsheets/fs204/en/#