Overview on Hepatitis B virus

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Abstract: Hepatitis B is an infectious illness caused by hepatitis B virus (HBV). The disease has caused epidemics in parts of Asia and Africa, and it is endemic in China. About a third of the world's population, more than 2 billion people have been infected with thehepatitis B virus. This includes 350 million chronic carriers of the virus. This paper offers an overview of hepatitis B virus.
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Intoduction:

Hepatitis B is an infectious illness caused by hepatitis B virus (HBV).[1] The disease has caused epidemics in parts of Asia and Africa, and it is endemic in China.[2] About a third of the world's population, more than 2 billion people, have been infected with thehepatitis B virus.[3] This includes 350 million chronic carriers of the virus.[4]

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, itching, dark urine, and then progresses to development of jaundice. The illness lasts for a few weeks and then gradually improves in most affected people. A few patients may have more severe liver disease (fulminant hepatic failure), and may die as a result of it. The infection may be entirely asymptomatic and may go unrecognized. [5]Chronic infection with hepatitis B virus may be either asymptomatic or may be associated with chronic hepatitis, leading to cirrhosis over a period of several years. This type of infection dramatically increases the incidence of hepatocellular carcinoma (2-5% after development of cirrhosis) . 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.[6]

Transmission: Transmission of hepatitis B virus results from exposure to infectious blood or body fluids containing blood. Possible forms of transmission include unprotected sexual contact, blood transfusions, re-use of contaminated needles & syringes, and vertical transmission from mother to child during childbirth. Without intervention, a mother who is positive for HBsAg confers 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.[7] However, at least 30% of reported hepatitis B among adults cannot be associated with an identifiable risk factor.[8]

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. The virus gains entry into the cell by binding to an unknown receptor on the surface of the cell and enters it by endocytosis. 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 and transformed into covalently closed circular DNA (cccDNA) that serves as a template for transcription of four viral mRNAs. 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 which 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 synthesizes DNA via its reverse transcriptase activity. [9]

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. [10] Most genotypes are now divided into subgenotypes with distinct properties.[11] The genotypes have a distinct

geographical distribution and are used in tracing the evolution and transmission of the virus. Genotype A is associated with better response to interferon. Disease progression appears to be slower in genotype B and C.[10]

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 to the hepatitis B core antigen (*anti-HBc IgM*) may be the only serological evidence of disease .[12]

Shortly after the appearance of the HBsAg, another antigen named as the 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*). A person negative for HBsAg but positive for anti-HBs has either cleared an infection or has been vaccinated previously.[12]

Individuals who remain HBsAg positive for at least six months are considered to be hepatitis B carriers.[13] Carriers of the virus may have chronic hepatitis B, which would be reflected by elevated serum alanine aminotransferase levels and inflammation of the liver, as revealed by biopsy. Carriers who have seroconverted to HBeAg negative status, particularly 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.[14] 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.[15] At least two laboratory tests over 12 months is fundament to establish a correct diagnosis and the indication for treatment, liver biopsy is recommended either when liver enzymes are abnormal or HBV DNA > 2000 Iu/ml(10000 copies/ml).[16]

Table 1. Chronic hepatitis B is a dynamic infection with five major phases: [16]

	HBs Ag	HB DNA	Liver enzymes	Histology
Immune tolerant	+ ve	High level	Normal	Mild or no necroinflammation
Immune reactive	+ ve	Low level	Increased and or fluctuating	Moderate to severe necroinflammation
Carrier	+ve	Very low level	Normal	Mild or nonecroinflammation
HB E Ag –ve hepatitis	+ve	Fluctuating	Increased often fluctuating	Moderate to severe necroinflammation
HBS Ag –ve	-ve	- ve	Normal	No necroinflammation

All pregnant women, persons need immunosuppressive therapy, persons undergoing renal dialysis, HCV patients, persons with elevated liver enzymes, with multiple sexual partner or history of sexually transmitted diseases, addicts, health care worker. Testing for HBsAg and anti HBs should be performed, and seronegative persons should be vaccinated [16]

Prevention: Hepatitis B is transmitted through body fluids; prevention is thus the avoidance of such transmission: unprotected sexual contact, blood transfusions, re-use of contaminated needles and syringes, and vertical transmission during child birth. Infants may be vaccinated at birth. Several vaccines have been developed by Maurice Hilleman for the prevention of hepatitis B virus infection. These rely on the use of one of the viral envelope proteins (hepatitis B surface antigen or HBsAg). The vaccine was originally prepared from plasma obtained from patients who had long-standing hepatitis B virus infection.

However, currently, it is made using a synthetic recombinant DNA technology that does not contain blood products. One cannot be infected with hepatitis B from this vaccine.[17] Following vaccination, hepatitis B surface antigen may be detected in serum for several days; this is known as vaccine antigenaemia.[18] The vaccine is administered in either two-, three-, or four-dose schedules into infants and adults, which provides protection for 85–90% of individuals.[19] postvaccination testing should be performed at 9-15 months of age in infants of carrier mothers and 1-2 months after the last dose in other persons. Protection has been observed to last 12 years in individuals who show adequate initial response to the primary course of vaccinations, and that immunity is predicted to last at least 25 years.[20]

Shi, et al showed that besides the WHO recommended joint immunoprophylaxis starting from the newborn, multiple injections of small doses of hepatitis B immune globulin (HBIg, 200–400 IU per month), or oral lamivudine (100 mg per day) in HBV carrier mothers with a high degree of infectiousness ($>10^6$ copies/ml) in late pregnancy (the last three months of pregnancy),[21] effectively and safely prevent HBV intrauterine transmission, which provide new insight into prevention of HBV at the earliest stage.

Treatment: Acute hepatitis B infection does not usually require treatment because most adults clear the infection spontaneously.[22] Early antiviral treatment may only be required in fewer than 1% of patients, whose infection takes a very aggressive course (fulminant hepatitis) or who are immunocompromised. [23]

Indication of treatment in chronic HBV infection

A: Combination of two of the following:

1: Increased liver enzymes.

2: HBV DNA >2000 Iu/ml or 10000 copies/ml.

2: Liver biopsy shows moderate to severe necroinfalmmation ≥ A2 and or F2.

B: Cirrhosis with and detectable HBV DNA. [16]

Although none of the available drugs can clear the infection, they can stop the virus from replicating, thus minimizing liver damage. Currently, there are seven medications licensed for treatment of hepatitis B infection: Nucleoside analogues (lamivudine, Telbivudine and Entecavir) Nucleotide analogues (Adefovir, Tenofovir and Emtricitabine) and Pegylated interferon alpha-2a or alpha 2b once weekly. [16]

A: Interferon is an antiviral agent with antiproliferative and immunomodulatory agent that is administered by subcutaneous injection once weekly. However, some individuals are much more likely to respond than others (HB eAg +ve, genotype A or B, low viraemia ($<10^7$copies/ml), ALT > 3 times ULN), high activity score in histology).[24] 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.[24] Side Effects: Depression, muscle aches, fatigue, and low grade fevers, low white blood cell count, headaches, irritability, and thyroid dysfunction. Underlying autoimmune disorders may also be unmasked. [16]

B) Lamivudine: Is an oral nucleoside analog inhibits hepatitis B viral DNA synthesis. It is approved for use in adults and children and is usually tolerated well. Daily dosing of 100 mg reduces serum HBV-DNA to below detectable levels within 6 weeks. In HBeAg-positive patients, approximately 16% of treated patients seroconverted with the first year. This was associated with significant improvement in liver histology. Long-term treatment induces further HBeAg seroconversion, but overall clinical benefit is undermined by continuous emergence of drug-resistant YMDD mutants. YMDD mutants may cause a flare of hepatitis, resulting in deterioration of liver histology and, occasionally, liver failure. The most common side effects seen during treatment were headache; abdominal discomfort and pain; nausea and vomiting; diarrhea; muscle pain; sore throat; joint pain; fever or chills; and skin rash. [25]

C: Adefovir: Is a nucleotide analogue inhibits DNA polymerase activity and reverse transcriptase. This drug is administered orally on a daily basis and is typically well tolerated. The most common side effects observed were weakness, headache, stomach pain and nausea. very serious hepatitis if you stop taking it, nephrotoxicity, lactic acidosis. [16]

D:Baraclude: Nucleoside analogue reverse transcriptase inhibitor. The recommended dose of

Baraclide is 0.5 mg once daily in nucleoside-naïve adults, and 1 mg once daily in lamivudine-refractory adults. Baraclude should be administered on an empty stomach (at least 2 hours after a meal and at least 2 hours before the next meal). The optimal duration of treatment with Baraclude for patients with chronic hepatitis B infection and the relationship between treatment and long-term outcomes such as cirrhosis and hepatocellular carcinoma are unknown. Dosage adjustment is recommended for patients with a creatinine clearance of less than 50 ml/min, including patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Entecavir should be administered after hemodialysis. CAPD removed approximately 0.3% of the dose over 7 days. The most common adverse events of moderate to severe intensity among patients treated with Baraclude in clinical trials included: headache (4%), fatigue (3%), diarrhea (1%), and dyspepsia (1%). Therapy with Baraclude is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART). Before initiating Baraclude therapy, HIV antibody testing should be offered to all patients. [16]

D: Tenofovir: Is a nucleotide analogue reverse transcriptase and hepatitis B virus (HBV) polymerase inhibitor (NRTI). [16]

Lamivudine has the lowest barrier to viral resistance followed be Telbivudine, Adefovir has an intermediate efficacy (barrier to resistance). The most potent antiviral with the lightest barrier for resistance mutation are Tenofovir and Entecavir both may be the first line for treatment of CHB and the treatment of choice whenever resistance occurs. [16]

Treatment adjustment in case of resistance to antivirals. [16]

Resistance to	Treatment adjustment
Lamivudine	Switch to Adefovir or Tenofovir
Adefovir	If N236T mutation is present add Lamivudine or Entecavir or Telbivudine or switch to Tenofovir and Emtricitabine If A181V/T mutation is present add Entecavir or switch to Tenofovir
Entecavir	Add Tenofovir
Telbivudine	Add Tenofovir
Tenofovir	Add Lamivudine or Entecavir or Emtricitabine

Treatment of especial patients groups: [16]

1: Children: The majority of children are in an immune tolerant phase and should not be treated.

2: Liver cirrhosis: All cirrhotics should be treated with any detectable viraemia.

3: Liver transplantation: All HBV patients should be treated before transplantation regardless of ALT and HBV DNA levels. HBV DNA must be undetectable at transplantation. After transplantation long term treatment combination with NUCs and anti HBs immunoglobulin (HBIG).

4: Co infection with hepatitis C: Usually one virus dominate, often HCV dominate the treatment with pegyltaed interferon and ribavirin till sustained virological response, HBV can reactivate and thus need to be closely monitored, and eventually treated with NUCs.

5: Co infection with HIV: Treatment target both viruses (Tenofovir lamivudine, Entecavir and Emtricitabine) however (Adefovir and Telbivudine) are agents without activity on HIV replication.

6: Pregnancy: Antiviral treatment is to be avoided until the third trimester of pregnancy. Lamivudine reduce the risk of intra-uterine and perinatal transmission of HBV if given in addition to HB IG and vaccination within twelve hours of birth . This treatment allows a mother to safely breastfeed her child.

7: Immuno suppressed patients: Patients who will receive chemotherapy even for short period should be screened (HB SAg, HB c Ab, HBs Ab) HBV DNA if HB SAg is + ve. Vaccination should be given if all marker are – ve. Lamivudine should be given to (HB SAg +ve) carriers before and 12 months after cessation of chemotherapy, while HB c Ab +ve with –ve S Ag carriers should be followed up twice monthly without antiviral treatment. If reactivation occurs a potent NUC should be started.

8: Patients with chronic renal failure: Lamivudine may be the safest choice, with dose adjustement, in patients with renal failure. For renal transplant recipient the best drugs may be lamivudine or entecavir.

9: Health care workers especially those involved in invasive procedures should be treated with a potent NUC, if HBV viraemia ≥ 2000 IU/ml. [16]

Prognosis: Hepatitis B virus infection may either be 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[26]. 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.[27]

Hepatitis D (HDV) can only occur with a concomitant hepatitis B infection, because HDV uses the HBV surface antigen to form a capsid.[28] Co-infection with hepatitis D increases the risk of liver cirrhosis and liver cancer.[29] *Polyarteritis nodosa* is more common in people with hepatitis B infection.

Reactivation: Hepatitis B virus DNA persists in the body after infection and in some people the disease recurs.[30] Although rare, reactivation is seen most often in people with impaired immunity.[31] HBV goes through cycles of replication and non-replication. Approximately 50% of patients experience acute reactivation. Male patients with baseline ALT of 200 UL/L are three times more likely to develop a reactivation than patients with lower levels. Patients who undergo chemotherapy are at risk for HBV reactivation. The current view is that immunosuppressive drugs favor increased HBV replication while inhibiting cytotoxic T cell function in the liver.[32]

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