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A Review on Pathogenesis, Transmission, Diagnosis and Prevention of Hepatitis B infection

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ABSTRACT:

Hepatitis B infection is caused by the hepatitis B virus (HBV). A double-stranded virus of the hepadnaviridae family. It infects the liver, causing hepatocellular necrosis and inflammation. HBV infection can be either acute or chronic, and the associated illness ranges in severity from asymptomatic to symptomatic, progressive disease. Over two billion people are known to be infected with Hepatitis B virus. Hepatitis B disease is ranked among the ten top killer diseases, with over a million deaths recorded annually from chronic HBV infection and its complications: cirrhosis or primary liver cancer. Liver injury occurs through immune-mediated killing of infected liver cells. Hepatitis B disease has huge health, mortality and economic burden. This review was aimed at contributing to global knowledge on Hepatitis B infection with the objectives of controlling its spread through prevention and vaccination. The review was on the burden and epidemiology of HBV, it's Pathogenesis, Transmission modes, Signs and symptoms, Risk factors for Hepatitis B, Diagnosis, Drugs approved for the treatment of chronic hepatitis B and prevention of HBV infection. This review noted that HBV vaccination is very effective and remains the best way to prevent Hepatitis B infection. Vaccination should be administered to everyone, but especially those who are at risk. Infants should be vaccinated within 24 hours of delivery. The review noted that avoiding risky behaviours through the practice of safe sex, use of protective hand gloves when handling blood or other body fluids, not sharing personal items like nail cutter, clippers, razors, or toothbrushes, single use of only sterilized disposable needles or body piercing objects, and screening of pregnant women before child delivery are very significant in HBV prevention.

Keyword: Acute Hepatitis B, Chronic Hepatitis B, Risk factors, Symptoms, Transmission, Prevention.

INTRODUCTION

"Hepatitis" means inflammation of the liver. Hepatitis B is a contagious and potentially life threatening liver disease that results from infection with a pathogenic agent; the Hepatitis B virus. The enveloped DNA virus belongs to the family hepadnaviridae [1], its virions are double-stranded particles, measuring 40 to 42 nm in diameter [2]. With a genome of only 3200 base pairs, HBV is one of the smallest DNA viruses known. It has an outer lipoprotein envelope that contains three related envelope glycoproteins (or surface anti-gens) [3]. Hepatitis B virus (HBV) infection may develop to: chronic hepatitis, hepatic cirrhosis, or primary hepatic cancer. Infection with hepatitis B virus (HBV) is a worldwide problem. Over a million deaths are recorded annually from chronic HBV infection and its complications: cirrhosis or primary liver cancer [4]. Liver injury occurs through immune-mediated killing of infected liver cells. The body's immune response tries to get rid of the virus by killing the infected cells. It is this self-defence mechanism that does most of the damage to the liver over time [5]. HBV is a recognized oncogenic virus that confers a higher risk of developing Hepatocellular Carcinoma Cancer (HCC) [6]. Hepatitis B is a disease of significant health importance. Over two billion people are known to be infected with Hepatitis B virus. Hepatitis B disease is ranked among the ten top killer diseases [7]. Ott *et al*. [8], reported that more than 2 billion people alive today have serologic evidence of past or present HBV infection, while 250 million are chronically infected and are at risk of developing HBV-related liver disease. It was also reported that 15-40% of chronically infected patients will develop cirrhosis, progressing to liver failure and/or HCC during their lifetime [9]. The prevalence of hepatitis B virus infection is relatively high in Africa, having the second highest number of chronically HBV-infected individuals. Poynad [10], observed that HBV infection varies epidemiographically with Africa, Asia and the Western Pacific accounting for higher infection rates of ≥ 8%, Southern and Eastern Europe with 2 - 7.9 % infection rates, while Western Europe, North America and Australia infection rates lowest (≤ 2 %). The health and economic burden of hepatitis diseases in Nigeria is enormous, with high mortality. Nigeria is endemic for HBV infection with about 18 million known infected people [11].

Pathogenesis of HBV infection

Host–virus interaction, mediated by the adaptive immune response all together determines the outcome of HBV infection [12]. WGO [13], noted that the virus-specific T cell response is one of the key factors in the pathogenesis of HBV infection. The course and outcome of the disease may be influence viral variants. Hollinger and Liang [14], observed that the effect of host factors on the progression of disease is not well understood. Hepatitis B virus infections rarely become directly cytopathic, except in cases of extreme immune suppression [15]. There is no age specificity in the infection and development of the disease [16]. Acute (self-limiting) infection, fulminant hepatic failure, inactive carrier state, and chronic hepatitis with chances of progression to cirrhosis and hepatocellular carcinoma are the clinical course (but not necessarily sequential) of HBV infection [17]. Adults that acquire acute infection usually recover or can be managed by supportive therapy, but the chronic type is ultimately fatal [18]. The average incubation period of Hepatitis B is 60 to 90 days (range is 40 to 160 days)[19]. HBV replicates in the hepatocytes of humans and other higher primates but does not grow in artificial cell cultures. Kapoor *et al*.[20], observed that in acute hepatitis B, the disease may last from one to six weeks but may be prolonged and can be fulminate. The

progression from acute to chronic infection is largely influenced by the age of the person who comes in contact with the virus. A person is said to be chronically infected if the person's immune system is not able to clear the virus six months later after the initial exposure of HBV. NICE [21], explained that the course of chronic HBV infection can be divided into the following four phases based on markers of replicative or non-replicative disease:

i. the immune tolerant phase
ii. the immune clearance phase
iii. the immune control phase and
iv. immune escape.

Not all chronic patients experience all phases of persistent disease and patients can also move from an immune active to an inactive phase and vice versa [22].

Transmission of Hepatitis B

Hepatitis B viral infection is body-fluid borne. The virus can be transmitted through vehicles of human transmission, such as contact with blood or other body fluids of an infected person. It is spread predominantly by percutaneous or mucosal exposure to infected blood and various body fluids, including saliva, menstrual, vaginal, and seminal fluids [23]. Transmission occurs primarily in two forms: vertical (the passage of pathogens from mother to the baby during the period immediately before and after birth) or horizontal transmission (the spread of infectious agents between members of the same species that are not in a parent-child relationship, usually through contact with bodily excretions or fluids, such as sputum or blood, semen, and vaginal fluids that contain the agents) [24]. Chen and Chang [24], enumerated three mechanisms of HBV trans-mission from HBsAg-positive mothers to include: (i) trans-placental intra-uterine transmission; (ii) transmission during delivery by contact with maternal infected fluids in the birth canal; and (iii) post natal transmission from mothers to infants during child care or through breastfeeding. Although it has been observed that HBV can infect the fetus in utero, this is not common and is generally associated with antepartum haemorrhage and placental tears [25]. Beasley *et al*. [26], observed that the risk of perinatal infection is increased if the mother has acute hepatitis B in the second or third trimester of pregnancy or within two months of delivery. The Hepatitis B virus is 50–100 times more infectious than HIV. It is stable on inanimate object for at least 7 days, and can be passed through the exchange of body fluids [27].

Signs and Symptoms of Hepatitis B

The symptoms of "acute" Hepatitis B viral infection may range in severity from a very mild illness with few symptoms or asymptomatic, to a serious condition requiring hospitalization [28]. Acute Hepatitis B (also refers to as new infection) describes the initial stage of the disease, usually within the first 6 months after acquiring the Hepatitis B virus. Individuals with strong body defence mechanism may be able to fight the infection and eliminate the virus. However, the infection remains and leads to "chronic" or lifelong illness in others [28]. Chronic Hepatitis B describes the disease after 6 months of infection; the Hepatitis B virus remains in a person's body, causing serious health problems over time. Several cases of chronic Hepatitis B are asymptomatic. More than half of the patients at this stage are not aware of their Hepatitis B infection status. Nevertheless, they still performs the role of reservoir of infection; spreading the Hepatitis B virus to others [29]. In acute Hepatitis B disease, the symptoms vary significantly, depending on the overall health of the infected person. Bello *et al*. [29], listed the common symptoms of acute Hepatitis B to include: fatigue, loss of appetite, nausea, vomiting, fever, headache, muscle aches, joint pain, abdominal disturbances, grey-colored stool, dark urine and jaundice. Symptoms of acute Hepatitis B in adults usually manifest within three months of exposure and may persist for weeks or months.

Risks Factors for Hepatitis B

CDC [30] reported that any susceptible individual can acquire Hepatitis B, but people who are at greater risk, include those who engage in any of the following activities, or are characterized with any of these:

i. Have sexual contact with an infected person
ii. Heterosexual persons with multiple sex partners.
iii. Have a sexually transmitted disease
iv. Unvaccinated men who have sex with other men.
v. Commercial sex workers and those who patronize them
vi. Inject drugs or share needles, syringes, or other injection equipment
vii. Tattooing; body piercing; and acupuncture.
viii. Close household contact with an infected person.
ix. Patient on hemodialysis
x. Exposed to blood on the job
xi. Nosocomial exposure
xii. Use of inadequately sterilized syringes and needles.
xiii. Intravenous and percutaneous drug abuse
xiv. Infants born to infected mothers
xv. Renal dialysis patients

Diagnosis of Hepatitis B

The three primary markers (or measurable indicators) of HBV infection are:

i. the surface antigen (HBsAg), which indicates current disease
ii. total core antibody (HBcAb IgM and IgG), which indicates present or past infection; and
iii. antibody to the surface antigen (HBsAb), which indicates immunity.

HBsAg-positive specimens are diagnosed further using the following secondary markers:

i. the e antigen (HBeAg), which indicates high viral replication and infectivity
ii. the e antibody (HBeAb), which indicates low viral replication and low-to-moderate infectivity
iii. the IgM core antibody (HBcIM), which indicates current or recent disease.

The diagnosis of hepatitis B is done through clinical symptoms and laboratory examination. In general, there are general considerations in the diagnosis of hepatitis B. A person's history, age, risk factors, vaccination status and previous tests results should be used to guide appropriate testing. The diagnosis of HBV infection is made through blood testing [22]. Serological test can be performed on either serum or plasma. HBV antigens and antibody are stable at room temperature for days, 4°C for months, and frozen at -20°C to -70°C for many years. Today, automated enzyme immunoassays that depend on colurimetic or chemiluminescence signal measurement, care should be taken to avoid haemolysis of the sample as it may interfere with the ability of the assay accurately detect these markers. Besides, measures should be taken to avoid the degradation of the viral nucleic acid in the specimen, which can result in falsely low or no measurable viral load. Therefore, serum should be removed from the clotted blood within 4 hours of collection and stored at -20°C to -70°C [31].

The laboratory diagnosis of acute hepatitis B is made through the presence of IgM antibody to HBV core antigen (IgM anti-HBc). IgM anti-HBc is rapidly followed by IgG anti-HBc. Even though this occurs, IgM may persist for months to years and may even reappear during flares of chronic HBV. In self-limiting cases, there are presence of antibody to the hepatitis B

surface antigen (anti-HBs) which indicates recovery from infection. This usually appears weeks to months following disappearance of serum HBsAg. Markers of HBV replication-HBeAg and HBV DNA is also present during the initial phase of infection. They are also present in the chronically infected individual. HbsAg, HbeAg, and HBV DNA are not specific for acute infection [13].

Significance of viral markers in hepatitis B

Table 1: Significance of viral markers in hepatitis B

Antigens	
HBsAg	Acute or chronic infection
HBeAg	Acute hepatitis B Persistence implies: continued infectious state, development of chronicity increased severity of disease
HBV DNA	Implies viral replication Found in the serum and liver
Antibodies	
Anti-HBs	Immunity to HBV; previous exposure; vaccination
Anti-HBe	Seroconversion
Anti-HBc	
IgM	Acute hepatitis (high titre) Chronic hepatitis (low titre)
IgG	Past exposure to hepatitis B (HBsAg-negative)

Source: WGO [13]

Approved drugs for the treatment for CHB

List of drugs approved for the treatment of chronic hepatitis B are presented in table 2.

Table 2: Approved drugs for chronic hepatitis B

Family/drug name	**Status**	**Global access: percentage on national essential medicines list** *
Interferons (IFNs)- immunomodulators		
Activate a host of genes with antiviral, antiproliferative, and immunostimulatory activities		
Interferon alfa-2b	FDA approval 1991	54.0 %
Peginterferon alfa-2a	FDA approval 2005	50.8%
Peginterferon alfa-2b	FDA approval 2011	
Nucleoside/nucleotide analogues (NAs)		
Inhibit the DNA polymerase of HBV and thus HBV replication		
Lamivudine	FDA approval 1998	66.7%
Adefovir dipivoxil	FDA approval 2002	34.1%
Entecavir	FDA approval 2005	34.9 %
Telbivudine	FDA approval 2006	23.8 %
Tenofovir	FDA approval 2008	48.4 %

*Reported percentages of WHO member states with drugs for hepatitis B on their national essential medicines lists or subsidized by their governments

Source: WGO [13]

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