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# Prevalence of Hepatitis B Virus Infection among Jaundiced Children in Bangladesh: A study in Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh

Dr. Ahmed Rashidul Hasan[1], Prof. Syed Shafi Ahmed[2], Kamrun Nahar[3], Dr. Salahuddin Mahmud[4]

[1]RMO, Paediatric Gastroenterology, Dept. of Hepatology & Nutrition, Dhaka Shishu (Children) Hospital Dhaka, Bangladesh
[2]Professor, Paediatric Gastroenterology, Dept. of Hepatology & Nutrition, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh
[3] Classified Specialist in Paedatrics Oncology, Combined Military Hospital, Dhaka, Bangladesh
[4]Assistant Professor, Paediatric Gastroenterology, Dept. of Hepatology & Nutrition, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh

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***Corresponding author:** Dr. Ahmed Rashidul Hasan

**Abstract** **Original Research Article**

***Aim:*** To determine the prevalence of Hepatitis B Virus (HBV) among jaundiced children admitted in in the department of Hepatology & Nutrition, Dhaka Shishu (Children) Hospital Dhaka, Bangladesh. ***Study design:*** Cross-sectional study. ***Study duration*:** Aug. 2016 to Feb. 2017. ***Methods:*** A total number of 280 children with diagnosis of jaundice having age 1 to 15 years were included. Blood samples were taken and were sent to the central laboratory of the hospital for ELISA test. Data analysis was carried out using SPSS V10. Seropositivity of hepatitis B virus antigen was presented as frequency and percentage. Chi-square test was applied to determine the association of age groups and gender with HBV infection, taking p-value ≤0.05 as significant difference. ***Results:*** The mean age of children in this study was 8.66±4.00 years. There were 179(63.9%) males and 101(36.1%) females. The mean duration of jaundice in this study was 7.9±6.21 days. The mean serum bilirubin levels in jaundice patients were 8.09±2.91mg/dl. Hepatitis B virus (HBV) infection was diagnosed in 51(18.2%) patients. There were 38(21.2%) males and only 13(12.9%) females who were positive for hepatitis B virus antigen (p-value 0.05). ***Conclusion:*** A higher rate of seropositivity of hepatitis B virus (18.2%) is found in children of jaundice. HBV is more common among males as compared to females.

**Keywords:** Jaundice, Hepatitis B virus infection, Gender, Bangladesh.



## INTRODUCTION

Hepatitis is a major health issue of both developed as well as developing countries. The prevalence of hepatitis B Virus (HBV) infection varies from country to country and even within a country. Hepatitis B virus infection has a close association with behavioral, host and environmental factors [1]. According to global estimates, about 350-400 million people are chronically infected with hepatitis B virus out of which about 80% are Asians[2,3]. The incidence of HBV virus in North America and Europe is about 1/1000 of normal population [3]. About 10 to 30 million people become infected with HBV every year worldwide and most of them are children and teenagers [4]. Hepatitis B virus is an important cause of acute or chronic liver disease and thus an important cause of mortality and morbidity worldwide [1, 5]. In developing countries like Africa and Asia about 2 billion people have markers of current or past HBV virus infection [6]. And about 15-25% of these people die due to chronic liver infections each year. Socio-economic factors and poorly developed health care system is the major contributor of ineffective control of HBV infection in developing countries [7]. HBV is transmitted through blood transfusion, very close contacts e.g. overcrowding, sexual contacts and by the use of common syringes, even without parenteral risk factors the infection can lead to fatal conditions like liver cirrhosis and hepatocellular carcinoma [8-10]. Martin *et al*. found 24% frequency of HBV infection in admitted Jaundice children having age 1 to 15 years [3]. However, we did not found any study in Bangladesh regarding prevalence of HBV in jaundiced children of our country. Therefore, we conducted this study to find the prevalence of HBV infection in children admitted to hospital due to jaundice. So that the exact frequency of

HBV infection can be obtained based on the results of this study and a large scale vaccination awareness program of HBV recommendations can be recommended to the concerned authorities regarding hepatitis B virus infection in children to insure proper vaccination of our children to prevent them from this infection.

***Management of Chronic Hepatitis B in Childhood***

Identification of risk factors & routes of its transmission will help to prevent global spread of the disease, especially in endemic regions [34]. Boys are affected more than girls, probably due to higher chance of exposure [35]. According to existing reports, there is no seasonal variation for primary HBV infection and it is more common among urban children than that of in rural children [36]. HBsAg is found in all body secretions and excretions. Transmission by percutaneous and per-mucosal exposure include transfusion of unscreened blood or blood products, sharing of unsterilized injection needles for intravenous medication, hemodialysis, acupuncture, tattooing and injuries from contaminated sharp instrument by hospital personnel[37]. Sexual and perinatal HBV transmission usually results from abraded mucous membrane exposure to infectious blood and body fluids [33]. About 70-90% of infants who are infected in their first few years of life become chronic carriers [38]. Perinatal transmission is more common in hyper-endemic areas of South East Asia, especially when HBsAg carrier mothers are also HBeAg positive [39]. Infection may also be transmitted between household contacts [32]. HBV is stable on environmental surfaces for at least 10 days. Indirect immunization of HBV will occur via inanimate objects like tooth-brushes, baby-bottles, toys, razors, intake utensils, hospital instrumentation and different objects by contact with secretion membranes or open skin wounds. Therefore, risk factors identification& active immunizationare the logical and rational approach for the management of HBV infection during a country like Bangladesh [1]. Breastfeeding has been shown not to contribute significantly to HBV transmission from infected mothers to infants who have received active and passive immunoprophylaxis. [40, 41]. Several drugs are used for the treatment of chronic infection. Lamivudine, adefovir, entecavir, tenofovir and interferon are commonly used in children. Treatment of chronic HBV infection by antiviral drugs is very costly. According to local market price, total treatment cost of oral antiviral drugs is about twenty thousand taka and that of interferon is about 2, 00,000 Taka. Moreover, outcome of treatment is also guarded. Sero-conversion (disappearance of HBeAg & appearance of anti HBe) occurs in about 17-32% cases if treated with oral nucleot(s) ide analogue and 58% cases if treated with interferon [42]. These dear medications with restricted treatment success don't seem to be appropriate for the poor individuals of Bangladesh. Therefore, risk factors identification& active immunizationare the logical and rational approach for the management of HBV infection during a country like Bangladesh.

***HBV life cycle***

Studies have shown that the species specificity and hepatotropic nature of HBV are thanks to a minimum of 2 completely different layers of cellular factors. The primary is that the hepatocyte-specific expression of the recently represented HBV receptor, human metallic element taurocholate cotransporting amide (hNTCP/SLC10A1) [Figure 2]. hNTCP is merely expressed on human hepatocytes, and mouse NTCP cannot be sure by HBV, that correlates with the lack of HBV to directly infect mouse hepatocytes. The second level of cell-specificity of associate degree HBV infection is managementled by hepatocyte-specific transcription factors like HNF1α and HNF4α; these control post-entry, downstream stages of the HBV life cycle. Proof for the extra role of intracellular factors for dominant the cell-specificity of associate degree HBV infection comes from the observation that humanized-mouse NTCP, during which the binding residues from mouse NTCP are replaced by hNTCP, permits binding of HBV to the receptor however doesn't lead to a productive HBV infection once expressed in mouse cells. Studies mistreatment infectious disease D virus (HDV), that could be a satellite virus requiring HBV envelope proteins for entry into a cell, incontestable that the seventy five aa at the N-terminal portion of the PreS1 domain of L-HBsAg ar needed residues answerable for binding to the infectious agent receptor. Additionally, it absolutely was shown that N-myristylation of the PreS1 domain is needed for infectivity, however not HBV particle assembly. In fact, a myristylated amide consisting of solely the primary forty seven aa of the preS1 domain is in a position to bind to hNTCP and inhibit the binding of HBV. Extra studies have urged a job for Liquaemin salt proteoglycans within the initial stages of HBV binding to hepatocytes, as well as the recent identification, mistreatment associate degree RNAi-based screen in Huh7 cells stably expressing hNTCP, of glypican five as associate degree HBV and HDV entry issue.

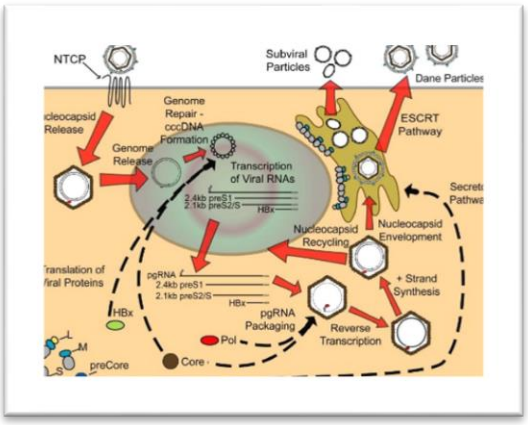


**Fig-1**

**Figure 1:** Life cycle of hepatitis B virus (HBV). Mature HBV virions enter hepatocytes through the sodium taurocholate cotransporting polypeptide receptor on the cell membrane. After release from the viral envelope, the nucleocapsid is then transported to the nucleus where the genome is repaired to form covalently-closed circular DNA (cccDNA). Using cccDNA as the template, viral RNAs are transcribed and exported into the cytoplasm where they are translated to form the viral proteins. Additionally, pregenomic RNA (pgRNA) is packaged by core protein, along with the polymerase protein, and the viral genome is replicated through reverse transcription of the pgRNA to form the - strand, followed by partial synthesis of the + strand. Mature nucleocapsids can then either be recycled back to the nucleus to maintain a pool of cccDNA, or enveloped and secreted through the ESCRT pathway. See text for a more detailed description of viral life cycle.

# METHODS

This cross-sectional study was conducted in the department of Hepatology & Nutrition, Dhaka Shishu (Children) Hospital Dhaka, Bangladesh from Aug. 2016 to Feb. 2017. A total number of 280 children with confirmed diagnosis of jaundice, age 1-15 years, and of any gender were selected. Children pre-vaccinated with hepatitis B virus infection and those suffering from any type of malignancy. Hepatocellular carcinoma or gastro-intestinal carcinoma was excluded. An informed consent was signed by all children or their parents. The approval from ethical committee of Jinnah hospital was taken. Clinical history regarding age of children, duration of jaundice and other relevant information regarding study was taken from the parents or the children itself. Blood sample were taken from every children by a phlebotomist and were sent to the central laboratory of the hospital for ELISA test. Data analysis was carried out using SPSS V10. Mean and standard deviation was calculated for age of children, serum bilirubin levels and duration of jaundice. Frequency and percentage were calculated for gender and seropositivity of hepatitis B virus antigen.

***Natural history of chronic hepatitis B (CHB) infection***

CHB infection evolves through five phases. All patients may not experience all phases and phases may not be sequential. Duration of phases varies and reversion of phases may occur. Phases are: immune tolerant phase, immune reactive phase, inactive carrier state, HBeAg negative CHB phase and HBsAg negative phase [43, 44].

| **Different** | **HBsAg** | **HBeAg** | **antiHBe** | **HBV DNA** | **ALT** | **Necro** |
|---|---|---|---|---|---|---|
| Phase | | | | | | inflammation |
| | | | | | | |
| Immune Tolerant | + | + | - | High | Normal | Mild/no |
| Immune Reactive | + | + | - | High | Raised | Moderate/ |
| | | | | | | severe |
| Inactive Carrier | + | - | + | Low/ | Normal | Mild/no |
| | | | | undetectable | | |
| HBeAg–ve CHB | + | - | +/- | Fluctuating | Fluctuating | Active |
| HBsAg -ve | - | - | - | Undectable of | Normal | No |
| | | | | very low | | |

**Immune tolerant phase**

Itis characterized by host immune tolerance though there is active viral replication. This phase is long in perinatally acquired infection, even may be 40 years or more. In this phase HBeAg is positive and Anti HBe is negative, serum HBV DNA is>20,000 IU/ml and there is persistently normal ALT. This phase is highly contagious because of high viraemia[45].

**Immune reactive phase**

In this phase host immune response is strong and reacts against virus infected hepatocytes. Here HBeAg is positive and begins to clear. HBeAg clearance rate is 10-15% per year. Anti HBe begins to become positive in the later part of this phase. Episodic flare of anti- HBcIgM occurs that may cause confusion with acute hepatitis [43]. Serum HBV DNA is >2000 IU/ml and there is persistent or intermittent elevation of ALT. This phase may last from several weeks to several years [47].

**Inactive carrier state**

These phase also known as low replicating phase. In this phase patients are HBeAg negative, Anti-HBe positive, Serum HBV DNA undetectable or low and there is persistent normal ALT. Liver biopsy shows absence of significant hepatitis. Here patients are asymptomatic. Minimum 1 year follow-up with normal ALT and low serum HBV DNA are needed to declare a patient as inactive HBV carrier. This phase has favorable long term outcome with low risk of cirrhosis and HCC. But about 10% of patients of this phase may reactivate to HBeAg positive or negative CHB infection [43, 44].

**HBe Ag negative CHB phase**

This phase followssero-conversion from HBeAg to anti HBe during immune reactive phase or may develop many years after inactive carrier state. It represents the reactivation of CHB. It may be due to pre-core mutation. Patient may be HBeAg positive or HBeAg negative. There is persistent or intermittent elevation of ALT. Patients of this phase have active liver disease and may progress to cirrhosis, hepatic de-compensation and HCC [47].

**HBsAg negative phase**

Thisphase is characterized by absent of both HBsAg & HBeAg in blood. HBV DNA becomes undetectable. Though HBV DNA is cleared off the blood it may present in hepatocytes. Such occult HBV infection may reactivate after immunosuppressive therapy. Mean annual rate of sero-conversion of HBsAg is 0.5-1% in sero-converted case [43].

***Clinical presentations of CHB infection***

Patients of CHB are mostly asymptomatic. In one study, history and clinical examination of patients of CHB showed that 56.7% were asymptomatic, 40% had nausea or vomiting, 35.5% abdominal pain, 15.3% jaundice, 21.1% hepatomegaly, 7.8% splenomegaly, 5.6% hematemesis or melena and 6.7% had ascites [48]. Clinical manifestations of CHB can be described in four overlapping stages. These are early progressive liver disease, progressive liver disease, advanced liver disease with complications and extra-hepatic manifestations. In early or slowly progressive liver disease stage, symptoms are nonspecific. Individuals frequently complain of anorexia, nausea, tiredness, abdominal discomfort and right upper quadrant pain. Physical examinations reveal no finding or only hepatomegaly. Some of the stigmata of chronic liver disease may be present. In the stage of progressive liver disease, there may be episodic hepatic flare along with symptoms of early disease. In this stage, common signs are hepatomegaly, mild jaundice and peripheral stigmata of chronic liver disease. Jaundice, ascites, coagulopathy, encephalopathy and fetor hepaticus may present. Complications like infection, portal hypertension, hepato-renal syndrome, hepato-pulmonary syndrome may develop in this stage. Extra-hepatic manifestations involve hematological, renal, rheumatological, dermatological, endocrine and neurological systems [49].

***Individuals who should be screened for HBV infection***

- Pre-vaccination screening
- Infant born to HBsAg positive mother
- Household contacts of HBV carriers
- Patients needing immunosuppressive therapy
- Before procedure, blood or organ donation
- Individuals who have used recreational or intravenous drugs
- Children infected with HIV
- Patients with chronic renal failure needing dialysis
- Children with raised transaminase for which causes are not identified
- All pregnant women
- Sexual contacts of HBV carriers

***Investigations***

Complete blood count (CBC) is usually normal. Macrocytic anemia is typically found in chronic liver disease but microcytic or normocytic anemia may also present. In case of hyper-splenism resulting from portal hypertension, pancytopenia may be found. Liver function tests (LFT) may be normal in early CHB infection. Commonly done LFTs are serum alanine aminotransferase (ALT), pro-thrombin time (PT), serum bilirubin and serum albumin. ALT is raised in immune clearance phase and in HBe Ag negative CHB cases. Viral markers e.g. HBsAg, Anti-HBcIgM, HBe Ag, Anti-HBe and HBV DNA, should be evaluated. In CHB infection HBsAg is positive but anti-HBcIgM is usually negative. HBe Ag is always positive in immune tolerance phase and HBeAg is usually negative inHBeAg negative CHB cases. Anti-HBe becomes positive when HBe Ag is negative. Patients infected with genotype D and infected with pre-core mutant virus tend to be HBe Ag negative butwith high HBV DNA titre[25]. Ultrasonography of hepato-biliary system is usually normal in early stage but increased echogenicity and evidence of portal hypertension may be found as the disease progress. Liver biopsy findings composed of summation of 4 individual scores: Peri-portal ± bridging necrosis, intra-lobular degeneration.

***Treatment of CHB***

Goals of Treatment: Goals of therapy are to reduce viral replication, to minimize liver injury, to reduce consequence of liver injury like cirrhosis & hepatocellular carcinoma (HCC) and to reduce infectivity of HBV[47]. Predictive of positive response embody high pretreatment elevation level, low pre-treatment HBV desoxyribonucleic acid [47]. Treatment is successful when there is low or undetectable HBV DNA, negativisation of HBeAg, sero-conversion to Anti- HBe, normalization of aminotransferase and reduction of necro-inflammation. A case is called cure when there is absence of HBsAg, undetectable HBV DNA and absence of HBeAg[46].

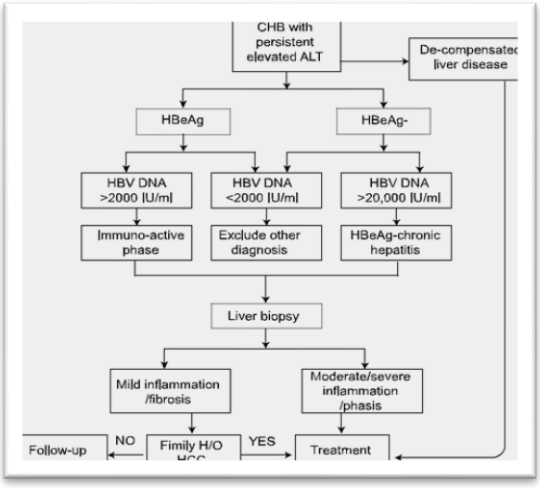


**Fig-2: Treatment algorithm of pediatric patient with CHB. Taken with permission from Paganelli *et al.* [29]**

***Indications for anti-viral therapy***

**Following criteria should be fulfilled to start antiviral therapy**

Chronic HBV infection: a) HBsAg positive for>6 months or more b) HBsAg positive and Anti-HBcIg M negative in one occasion, 2) Active hepatic inflammation:a) raised ALT for 6 months >1.5 ULN or >60 IU/L whichever is lowerb) Histological evidence of chronic hepatitis: moderate to severe inflammation and fibrosis, 3)Viral replication: a) HBV DNA >2000 IU/ mland/or b) HBe Ag positive. There are some special circumstances where treatment of CHB can be given in absence of standard criteria. These conditions are cirrhosis (compensated/ decompensated), chemotherapy, immuno-suppression, presence of co-infection (HBV-HIV), family history of HCC and pregnant women with high viral load [47]. In patient with cirrhosis the goals of antiviral therapy are to prevent liver disease progression to decompensated cirrhosis, development of HCC and liver related death [46]. Antiviral treatment in cirrhotic patients are not based on ALT because ALT may be normal in advanced liver disease. Treatment in cirrhotic children can be started even if the HBV DNA is low. Treatment with interferon can't be given in decompensated chronic liver disease patients because interferon may precipitate sepsis and liver failure. Treatment with nucleot(s) ide analogues are the preferred drug therapy. Here drugs are continued for indefinite period of time [50, 56]. Three year survival is 25% without therapy & 85% with therapy.

***Drugs currently recommended treating CHB***

Nucleot(s) ide analogues

- lamivudine,
- adefovir
- entecavir
- tenofovir

**Conventional interferon alfa (IFNa)**

***Lamivudine***

Lamivudine is the commonly used antiviral drugs. It is an oral drug.These drugs are cheap. It can be used in decompensated state of chronic liver disease and has no significant side effect. Sero-conversion occurs in 23% of cases following 52 weeks of treatment. Recommended duration of treatment is at least 1 year and should be continued for 6 more months after HBeAg seroconversion [32, 45]. Long term lamivudine therapy do not significantly increases sero-conversion rate rather there is chance of development of mutant strain. Chance of development of mutant strain and chance of relapse following stoppage of therapy are more with lamivudine. Viral resistance develop in 16% of cases after 1 year of therapy and 76% after 5 years therapy [52]. Therefore the use of lamivudine is limited due to occurrence of resistance. Dose- 3 mg/kg/day, highest dose is 100mg/day.

**Advantages**

- Cheap, - Less side effect, - Oral administration, - Usable in 3rd trimester of pregnancy, - Can be used in decompensated chronic liver disease

**Disadvantages-**

- High resistance rate (increased ifmore time of treatment), - Sero-conversion rate is low

Adefovir: Adefovir is also an effective antiviral drug in children. This drug is cheap and safe but nephrotoxic. Mutation associated with adefovir resistance was less common and lamivudine resistant mutants are susceptible to adefovir. As a single drug antiviral therapy it is not suitable because of its modest antiviral suppression effects and its renal toxicity. It is commonly used alone or in combination with lamivudine in lamivudine resistant cases. Drug resistance develops in 29% of cases after 5 years of treatment with adefovir. HBeAg seroconversion can be achieved in 30–37 % after 3–5 years of adefovir (ADV) treatment [53].
Dose- 0.3mg/kg/day in <6 years, 0.25mg/kg/day in >6 years and 10mg/day if age >12 years [37].

**Advantages**

- Cheap, -Oral administration, - Effective inlamivudine resistantcases.

**Disadvantages**

- Nephrotoxicity, - Sero-conversion rate is low.

**Tenofovir**

Tenofovir is a nucleotide reverse transcriptase inhibitor thatis more potent than adefovir in suppressing lamivudine resistant HBV. Tenofovir has been reported to achieve much higher biochemical, virological, and histological responses in both HBe Ag positive and negative patients, compared with adefovir and lamivudine. It has some side effects like renalinsufficiency, Fanconi syndrome and osteomalacia but no bone disease was detected at 3-year follow-up. Dose adjustment is required in patients with renal impairment. Tenofovir demonstrated safety and efficacy in patients with liver cirrhosis, and regression of cirrhosis during treatment with tenofovir was observed in 71 (74%) of 96 patients treated for 5 years: HBeAgsero-conversion in 40 % and HBsAg loss in 10 % [55]. Tenofovir was also found to be safe duringpregnancy as pregnancy category B.
Dose: 300 mg once daily.

**Advantages**

High response rate, - Few side effects, - Oral administration, - Usable in 3rd trimester of pregnancy

**Disadvantages**

Not approved for children <12 yr, - Reduced mineral density in children

**Entacavir**

Entacavir is recommended in children after 2 years of age [56]. It is a potent antiviral drug causing undetectable HBV DNA after 1 year of therapy and in 91% cases after 3 years of therapy. Chance of resistance is 0.8% after 3 years of entacavir therapy[57]. Dose- 0.015mg/kg/day, highest dose is 0.5 mg/day.

**Advantages-**

- Oral administration, - Low resistance rate

**Disadvantages**

- Abdominal discomfort, diarrhea, - Tachycardia, chest tightness

Interferon: Interferon produces their effects by antiviral effects and immune-modulatory action. Its efficacy is more than that of other oral drugs. Among the interferon, interferon alpha 2a is used to treat CHB infection. Pegylated interferon is used in adult but not recommended in children. Polyethylene glycol is linked to interferon molecule to make it long lasting. With interferon therapy there is 58% chance of HBV-DNA loss, 38% chance of HBeAg/anti-HBesero-conversion and 33% chance of HBsAg loss [57]. It is costly and associated with many side effects. It cannot be used in decompensated state of liver disease because it may cause infection and hepatic failure. HBeAgsero-conversion may occur at any time during or within 1 year of ending treatment with interferon alpha. Patient should not be declared as treatment failure or to start another drug until 1 year of treatment [46]. Dose- 6 MIU/$m^2$ thrice weekly by subcutaneous injection.

**Advantage**

- More effective antiviral drug, - Recommended for young children, - Short treatment (6 months treatment)

**Disadvantage**

Some side effects like liver failure,infection, flu like symptoms, depression, bone marrow suppression, hypothyroidism, - Hazardous parenteral administration,

- Not suitable to use indecompensatedcirrhosis or liver transplantation

***Predictive of positive response***

High pretreatment ALT level - Low pre-treatment HBV DNA- <20,000 IU/ ml - Younger age - Viral genotype B - Late acquisition of HBV infection - Higher hepatocellular inflammation.

***Special Populations***

Cirrhosis due to CHB (Compensated or decompensated): In case of cirrhotic patient, to prevent disease progression, to prevent HCC and to reduce liver related death anti-viral drugs should give. Nucleot(s) ide analogs are the drug of choice and drug should be continued lifelong.

Immuno-compromised children: Antiviral therapy is recommended in patient of CHB getting cancer chemotherapy or immunosuppressive therapy. Reactivation of HBV may occur following

immunosuppressive or cancer chemotherapy. Antiviral therapy should be started 2 weeks before initiation and continued for up to 6 more months after stoppage of chemotherapy or immunosuppressive therapy. Lamivudine or adefovir alone or in combination can be used [28].

Symptomatic acute hepatitis B: Although more than 95-99% of adults with acute HBV infection recover spontaneously and exhibit anti-HBs antibody sero-conversion without antiviral therapy, a small subset of patients may develop acute liver failure and accordingly, may benefit from NA treatment. Goal of treatment is to quickly reduce HBV- DNA &HBsAg and to reduce the risk of rejection of transplanted liver. Treatment should be continued upto 3 months after HBs Agsero-conversion Or 6 months after HBeAgsero-conversion without HBsAg loss. IFN is contraindicated because of the risks of worsening hepatitis and frequent side effects.

**Persons who are HBsAg-positive**

- Breast feeding is to be continued
- Screen family members & vaccinate when indicated
- Cover open wounds and scratches
- Clean blood spills with detergent or bleach
- Can share food and utensils
- Can participate in all activities including sports
- Should not be deprived of schools
- Should not be isolated from other children
- Should not share razors & toothbrushes
- Should not donate blood or organs

**Follow up**

- CBC is to be cheeked time to time for any neutropenia.
- Thyroid function test is to be done for hypothyroidism.
- Evaluation of renal functionthrough serum creatinine,

To assess adefovir toxicity. Serum ALT should be cheeked to assess drug response and post treatment flare [46]. HBe Ag and Anti-HBe should be cheeked 2 monthly for sero-conversion. Serial HBV DNA assay is needed to see the drug response. HBsAg status is cheeked in seroconverted patients. Ultrasonography of hepatobiliary system and alpha-fetoprotein are done yearly to see any malignant changes in liver [48].

***Prevention***

HBV infection is such an illness that it is difficult to treat, outcome of treatment is guarded and morbidity and mortality is high. That is why prevention is better than cure. This infection can be prevented by active immunization with vaccination, immune-prophylaxis of babies of HBsAg positive mothers, post-exposure prophylaxis and health education about the transmission of disease. Vaccine should be initiated immediately after birth [53]. Active immunization of children by vaccination is the best way of prevention of infection. Hepatitis B vaccination has been included in EPI schedule since 2005. For infants & children d”19 years, the dose of HB vaccine is 10µg (0.5ml) intramuscularly on anterolateral aspect of thigh/deltoid or subcutaneously. There are two dose schedules. One is 3-dose schedule: 0, 1, 6 months and another is 4-dose schedule: 0, 1, 2, 12 months. After first dose of vaccine 30-50% protection occurs, 75% protection after 2$^{nd}$ dose and 96% protection after 3$^{rd}$ dose of vaccine. Course of vaccination should never be started again when a schedule dose is missed or postponed, but should be completed in due course [63]. Immuno-prophylaxis is needed for the babies of HBV infected mother. If the birth weight of baby is e”2000 gm., three doses of vaccine on 0, 1 and 6th month and Hepatitis B immunoglobulin (HBIg) at birth is to be given. For babies of birth weight less than 2000 gm., four doses of vaccine on 0, 1, 2 and 7th month (one extra dose) along with HBIg at birth is recommended. Efficacy of immuno-prophylaxis is 90%, if only vaccine is given to babies of HBeAg negative carrier mother. Efficacy of immuno-prophylaxis is 75%, when vaccine only given to HBeAg positive carrier mother and efficacy is 85-95%, if vaccines along with HBIg are given to HBeAg positive carrier mother [64, 66]. Causes of failure of immune-prophylaxis (10-15%) are intra-uterine infection (5-10%).

## RESULTS

In this study, a total number of 280 patients were included. The mean age of children was 8.66±4.00 years. There were 179(63.9%) males and 101(36.1%) females. The mean duration of jaundice in this study was 7.9±6.21 days. The mean serum bilirubin levels in jaundice patients were 8.09±2.91 mg/dl. Hepatitis B virus infection was diagnosed in 51(18.2%) patients. while there were 229(81.8%) patients who were having jaundice due to other causes instead of hepatitis B. The children were divided into three groups on the basis of age (from 1-5 years, 6-10 years and 11-15 years). There were 14(17.7%) children in age group 1-5 years who were diagnosed of having hepatitis B virus infection. And there were only 20(17.9%) children in age group 6-10 years who were diagnosed with hepatitis B virus infection and only 17(19.1%) children in age group 11-15 years were diagnosed of having hepatitis B virus infection. This difference in the frequency of hepatitis B virus infection was not statistically significant (P-value 0.97). There were 38(21.2%) males and only 13(12.9%) females who were positive for hepatitis B virus antigen (p-value 0.05) [Table 2]. HBs Ag positivity indicates an ongoing HBV infection ora newly infected patient. It the sole serologic marker detected during the first 3-5 weeks after infection.[34]After recovery from HBV, it usually disappearswithin 3-4 months, and anti-HBs develops. The global prevalence of HBV infection fluctuates broadly and its endemicity ranges from high

(≥8%) to intermediate (2-7%) and low (<2%) [35]. In our study, we found 18.2% prevalence of HBV in jaundice children presenting at Jinnah Hospital Lahore. Nath *et al.* conducted a study in Katihar, India, and these authors found 24% prevalence of HBV infection in children with jaundice [36]. The prevalence of HBV in healthy children has been reported to be 0.22% in Saudi Arabia and 0.76% in Brazil [27, 37]. Many other countries have also reported similarly low prevalence of HBV in healthy children. However, the prevalence of HBV is very high among jaundice children. In our study, there were 74.5%males and only 25.5% females in whom HBs Ag was positive.

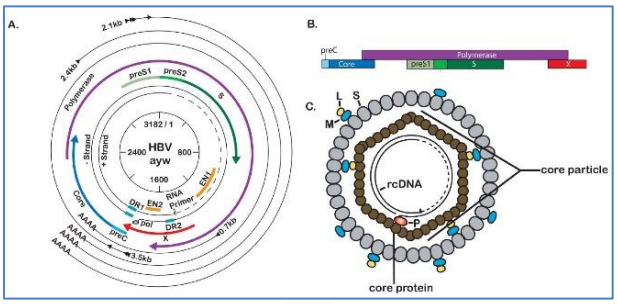


**Fig-3**

**Figure 3:** Molecular biology of hepatitis B virus (HBV). (A) Scaled depiction of the HBV (genotype ayw) genome. Internal circle shows genomic position relative to EcoRI site at position 1. Partially double-stranded genome is depicted with attached RNA primer and polymerase protein. Open reading frames (ORFs) are indicated by the thicker, colored lines. The outermost black circles represent the viral transcripts with the shared polyadenylation site; (B) schematic representation of the overlapping nature of the HBV ORFs; (C) the mature HBV virion (Dane particle) consists of two main parts: a nucleocapsid (or core particle) consisting of a partially double-stranded DNA genome bound to polymerase (P) and encapsidated by dimers of core protein, and a viral envelope consisting primarily of S-HBsAg (S), with an intermediate amount of M-HBsAg (M) and lower levels of L-HBsAg (L) Transcription of HBV RNAs is driven from specific promoter sequences within the viral genome. At least some of the hepatotropic restriction of HBV can be attributed to transcriptional activation by hepatocyte-specific transcription factors. For example, activation of the Enhancer I/HBx promoter is a required first step in viral transcription, as this is believed to enhance transcription from downstream promoters. A number of the transcription factors that have been mapped to the EN1/HBx promoter are liver specific, including hepatocyte nuclear factor (HNF) 1, HNF3, and HNF4. Many of the transcription factor binding sites that have been identified within the 4 promoter regions of HBV are for transcription factors that are activated by HBV proteins, oftentimes HBx, implying a specific cascade of transcription. Transcription factor-mediated regulation of HBV transcription has been reviewed in more detail elsewhere.

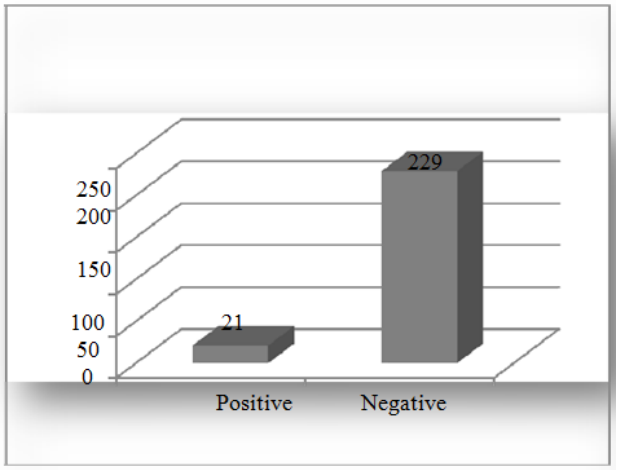


**Fig-4: Frequency of Hepatitis B virus infection**

**Table-1: Baseline characteristics (n=280)**

| Age (years) | Percentage |
|---|---|
| Mean | 8.66 |
| S.D. | 4.00 |

| | |
|---|---|
| Gender | |
| Male | 179 (63.9%) |
| Female | 101 (36.1%) |
| **D**uration of jaundice (days) | |
| Mean | 14.9 |
| S.D. | 12.21 |
| Serum bilirubin levels (mg/dl) | |
| Mean | 8.09 |
| S.D. | 2.91 |

**Table-2: Association of age and gender with HBV infection (n=280)**

| Age Groups | Hepatitis B | | P |
|---|---|---|---|
| | Present | Absent | value |
| 1-5 Years | 14 (17.7%) | 65 (82.3%) | 0.97 |
| 6-10 Years | 20 (17.9%) | 92 (82.1%) | |
| 11-15Years | 17 (19.1%) | 72 (80.9%) | |
| Gender | | | |
| Male | 38 (21.2%) | 141(78.8%) | 0.05 |
| Female | 13 (12.9%) | 88 (87.1%) | |

## DISCUSSION

HBV infection is a worldwide health problem with higher burden on developing countries like Bangladesh [33]. Bangladesh is a high disease burden country of hepatitis A to E, with higher mortality rate due in hepatitis B, C and D. No or very few data is available regarding prevalence of HBV in jaundiced children in Bangladesh. In current study, we evaluated the prevalence of HBV in children with jaundice. In Bangladesh, After HEV, HBV is the second most common cause of viral hepatitis. HBs Ag positivity indicates an ongoing HBV infection ora newly infected patient.It the sole serologic marker detected during the first 3-5 weeks after infection [34]. After recovery from HBV, it usually disappearswithin 3-4 months, and anti-HBs develops. The global prevalence of HBV infection fluctuates broadly and its endemicity ranges from high (≥8%) to intermediate (2-7%) and low (<2%)[35]. In our study, we found 18.2% prevalence of HBV in jaundice children presenting at Jinnah Hospital Lahore. Nath et al. conducted a study in Katihar, India, and these authors found 24% prevalence of HBV infection in children with jaundice [36]. The prevalence of HBV in healthy children has been reported to be 0.22% in Saudi Arabia and 0.76% in Brazil [27, 37]. Many other countries have also reported similarly low prevalence of HBV in healthy children. However, the prevalence of HBV is very high among jaundice children. In our study, there were 74.5%males and only 25.5% females in whom HBsAg was positive. In a study by Naz *et al*. [38], 68.3% males and only 31.7% females were HBsAg positive. Ahmad *et al*. in 2007 also announced a high predominance 64% in male children than female (36%) [39] Zubair *et al*. in 2010; conducted a study on recurrence of hepatitis B infection in children havingchronic liver disease and discover a high 54% prevalence in male than females (46%)[40]. Nwokediuko *et al*. in 2010; likewise detailed an altogether higher (79.2%) disease rate in male when contrasted with the female (20.8%) [41]. Khan *et al*. found a significant effect of age on the incidence of hepatitis B virus infection. In their study, Prevalence of HBV rose from 13.39% in teenage 1-5 years to a peak of 34.93% and 23.83 in people aged 6-10 years and 11-15 years respectively [42]. While it was less in very young 0-10 years 1.49% persons. Cisneros-Castolo *et al*. also reported that the prevalence of HBV infection is higher in patients up to the age of 15 years [43] higher prevalence of HBV infection in this age group may be due to their more contacts and gatherings with society than children and old age persons. In our study, there was no effect of age on frequency of HBV infection because we only took pediatric population in our study. Furthermore, Chronic HBV infection is also a major cause of hepatocellular carcinoma (HCC). The prevalence of HCC is escalating in the United States, Europe and in Bangladesh that has pulled a higher economic burden in these countries [44, 45]. So we should establish more effective and cost-effective management plan for control and management of viral hepatitis and its related complications. This will also help to reduce the hospital budgets [46]. Our study found that seroprevalence of HBV infection is high in jaundiced children. These results strengthens the significance of HBV vaccination at birth to inhibit peri-natal HBV transmission, and the inevitability of preventive measures such as educational activities to increase the awareness regarding HBV vaccination in childhood, to reduce the morbidity and mortality and the financial influence associated with the disease.

## CONCLUSION

Management of chronic HBV infection is difficult. Treatment outcome is guarded and sero-conversion occurs in 10-60% of patients. Moreover, commonly used drugs are costly. In a densely populated

country like Bangladesh where education is low, awareness of people through mass media may be considered as an effective way to prevent the spread of disease. Children are worst sufferer and they are the future of the nation. Special precaution should be taken to prevent transmission of the virus to them. Health education and vaccination at birth are the logical and practical approach to safeguard the children. A higher rate of seropositivity of hepatitis B virus (18.2%) is found in children of jaundice. HBV is more common among males as compared to females.

## RECOMMENDATIONS

As a priority, all children with CHB and clinical evidence of compensated or decompensated cirrhosis should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels.[56] HBeAg-positive patients with HBV DNA levels >20,000 IU/ml and elevated ALT for 3-6 months should be considered for treatment. HBe Ag-negativepatients withHBVDNA levels >2000 IU/ml and elevated ALT levels for 3-6 months should be considered for treatment. Cirrhotic child should also be treated irrespective of the ALT level, even if the viral load is below 20,000 IU/ml in HBeAg-positive patients or below 2000 IU/ml in HBeAg-negative patients. Tenofovir and entecavir are considered first-line therapies for treatment-naïve HBV patients because they are the most potent agents available with no or very low rates of antiviral resistance. Tenofovir is the first-line therapy for lamivudine-resistant HBV case. Entecavir should not be used in this setting due to the risk of development of entecavir resistance. In HBeAg-positive patients, nucleos(t)ide analog therapy should be continued until 12 months after HBeAgsero-conversion with close monitoring of HBV DNA and ALT levels following treatment withdrawl. In HBeAg-negative patients, nucleos(t)ide analog therapy should be continued indefinitely or until HBs Ag loss. HBV DNA should initially be monitored every 3 months to enable early detection of antiviral resistance and every 6 months once aviremia is achieved.

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