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Review Articles

Management of Chronic Hepatitis B in Childhood: A Comprehensive Guideline

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Abstracts

This guideline has been written to make familiar childhood hepatitis B virus (HBV) infection management for the pediatrician of Bangladesh. To develop this guideline, local & international data reviewing and several international practice guideline on the management of HBV infection were searched webs. This guideline has been developed to assist pediatric gastroenterologists, pediatricians and other health care providers for the management of HBV in Bangladesh. Objective of these guidelines is to give updated information in the management of HBV infection.

Key words: *Children, HBV, management.*

Introduction

Hepatitis B Virus (HBV) infection is prevalent worldwide. The lowest rates (0.2-0.5%) of HBsAg carrier rate is in countries having high standard of living, such as Britain, Canada, USA, Scandinavia and some other parts of Europe. In South East Asia, the prevalence of HBV infection is 8-20%.[1] Millions of people are chronically infected with HBV in Bangladesh and most infections occur during childhood.[2] Studies showed that the overall prevalence was about 3% in Bangladesh.[3] Although there is a paucity of information about a nation-wide survey regarding HBV prevalence in Bangladesh, published data show that about 5%-6% of apparently healthy individuals are HBV carriers in Bangladesh.[4-6]

In another study the prevalence of HBV infection among the students of a Girls' School of Dhaka city was found to be 2.3%,[7] it was 7% in multi-transfused thalassemic patients[8] and 3.6% in pregnant women of Dhaka city.[9] About 350 million people are chronically infected globally. Annually there are over 4 million acute cases of HBV infection and among them about 25% are carriers.[1]

HBV infection has different clinical manifestations depending on the patient's age at infection, immune status and the stage at which the disease is recognized. Children mostly remain asymptomatic and active. Jaundice or growth failure is rare and liver damage is usually mild during childhood. However serious sequele like cirrhosis and hepatocellular carcinoma may develop at any age.[10]

HBV vaccination is included in EPI since 2005. Though vaccine is available both commercially and through EPI, HBV infection is still a health problem and every year new cases are reported throughout

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the country.[11] Identification of risk factors & routes of its transmission will help to prevent global spread of the disease, especially in endemic regions.[12] Boys are affected more than girls, probably due to higher chance of exposure.[13] 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.[14] 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.[15] Sexual and perinatal HBV transmission usually results from abraded mucous membrane exposure to infectious blood and body fluids.[11] About 70-90% of infants who are infected in their first few years of life become chronic carriers[16]. Perinatal transmission is more common in hyper-endemic areas of South East Asia, especially when HBsAg carrier mothers are also HBeAg positive.[17] Infection may also be transmitted between household contacts.[10] HBV is stable on environmental surfaces for at least 7 days. Indirect inoculation of HBV can occur via inanimate objects like tooth-brushes, baby-bottles, toys, razors, eating utensils, hospital equipment and other objects by contact with mucous membranes or open skin wounds.[1]

Breastfeeding has been shown not to contribute significantly to HBV transmission from infected mothers to infants who have received active and passive immunoprophylaxis.[18,19]

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.[20] These expensive drugs with limited treatment success are not suitable for the poor people of Bangladesh. Therefore, risk factors identification& active immunizationare the logical and rational approach for the management of HBV infection in a country like Bangladesh.

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.[21,22]

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

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. Liver biopsy shows mild or no necro-inflammation and there is no or minimal fibrosis. This phase is highly contagious because of high viraemia.[23]

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.[21] Serum HBV DNA is >2000 IU/ml and there is persistent or intermittent elevation of ALT. Liver biopsy shows features of chronic hepatitis (HAIe"4) and there is more rapid progression to hepatic fibrosis. This phase may last from several weeks to several years.[25]

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.[21,22]

HBeAg 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. Liver biopsy shows features of chronic hepatitis (HAI e"4). Patients of this phase have active liver disease and may progress to cirrhosis, hepatic de-compensation and HCC.[25]

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.[21]

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.[26] Clinical manifestations of CHB can be described in four overlapping stages. These are early or slowly 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. Ultimately, CLD progress to advanced liver disease when different complications develop. 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.[27]

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 HBeAg negative CHB cases. Viral markers e.g. HBsAg, Anti-HBcIgM, HBeAg, Anti-HBe and HBV DNA, should be evaluated. In CHB infection HBsAg is positive but anti-HBcIgM is usually negative. HBeAg is always positive in immune tolerance phase and HBeAg is usually negative inHBeAg negative CHB cases. Anti-HBe becomes positive when HBeAg is negative. Patients infected with genotype D and infected with pre-core mutant virus tend to be HBeAg 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 & focal necrosis, portal inflammation and fibrosis. On the basis of histological activity index score cirrhosis may be classified as minimal, mild, moderate and severe.[27,28] Before and after giving anti-viral drugs creatinine should done routinely.

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[25]. Predictive of positive response include high pretreatment ALT level, low pre-treatment HBV DNA <20,000 IU/ml, late acquisition of HBV infection and higher hepatocellular inflammation[25]. 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.[24]

Treatment Algorithm of Hepatitis B

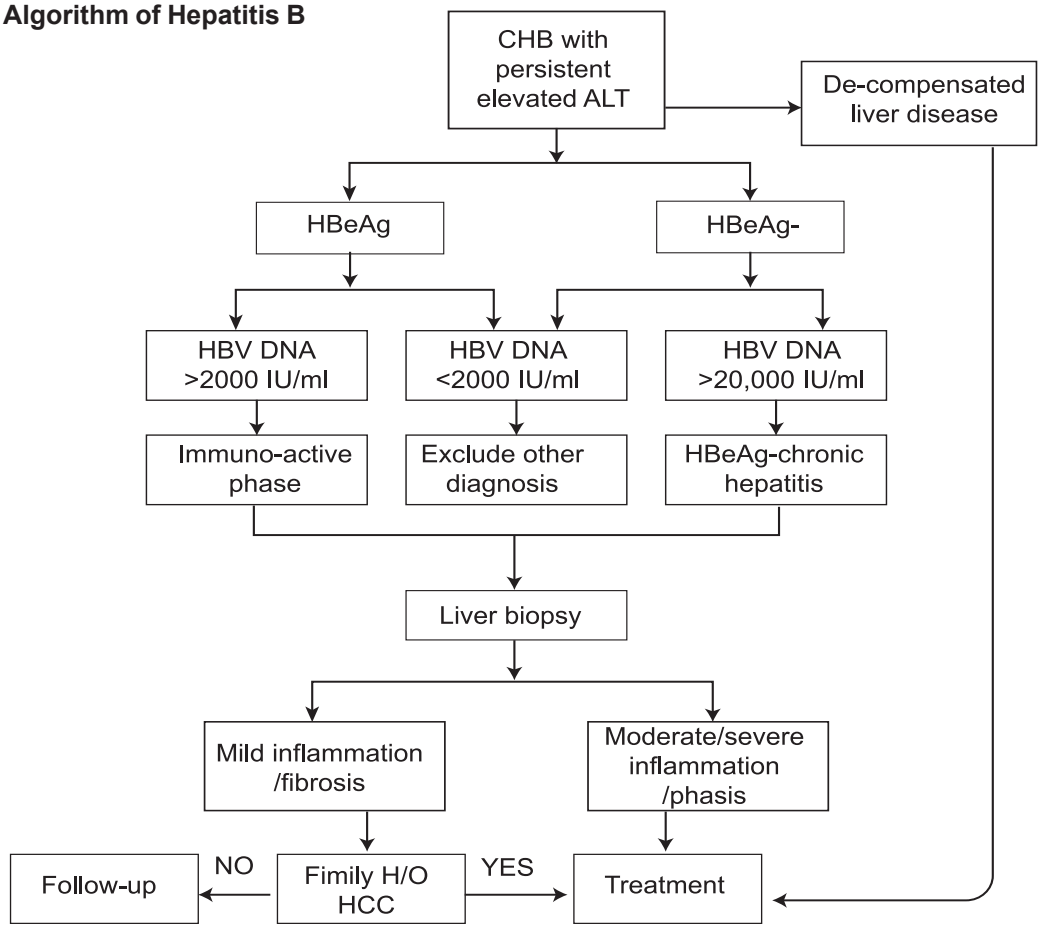

Fig.: *Treatment algorithm of pediatric patient with CHB. Taken with permission from Paganelli et al*[29]

Indications for anti-viral therapy:

Following criteria should be fulfilled to start antiviral therapy:

1) Chronic HBV infection: a) HBsAg positive for>6 months or more b) HBsAg positive and Anti-HBcIgM 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) HBeAg 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.[25]

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.[24] 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.[28,34] Five year survival is 25% without therapy & 85% with therapy.

Drugs currently recommended to treat CHB

1. Nucleot(s)ide analogues
   - lamivudine,
   - adefovir
   - entecavir
   - tenofovir
2. 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.[10,23] 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.[30] 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.[31]

Dose- 0.3mg/kg/day in <6 years, 0.25mg/kg/day in >6 years and 10mg/day if age >12 years.[15]

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 HBeAg 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 %.[33] 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[34]. 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.[35]

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.[35] 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[24].

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.

When to stop antiviral drugs

Duration of interferon therapy is 6 months. Oral antiviral drugs should be continued at least for one year and maintained for at least 12 months after HBeAgsero-conversion if there is no evidence of resistance or any severe adverse drug reaction. Children with HBeAg negative chronic hepatitis B, cirrhosis &who do not undergo HBeAgsero-conversion may need longer duration or even lifelong therapy.[24]

Recommendations

1. As a priority, all adults, adolescents and children with CHB and clinical evidence of compensated or decompensated cirrhosis should be treated, regardless of ALT levels, HBeAg status or HBV DNA levels.[34]
2. HBeAg-positive patients with HBV DNA levels >20,000 IU/ml and elevated ALT for 3-6 months should be considered for treatment.
3. HBeAg-negativepatients withHBVDNA levels >2000 IU/ml and elevated ALT levels for 3-6 months should be considered for treatment.
4. 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.
5. 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.
6. 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.

7. 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.
8. In HBeAg-negative patients, nucleos(t)ide analog therapy should be continued indefinitely or until HBsAg loss.
9. HBV DNA should initially be monitored every 3 months to enable early detection of antiviral resistance and every 6 months once aviremia is achieved.

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 HBsAgsero-conversion Or 6 months after HBeAgsero-conversion without HBsAg loss. IFN is contraindicated because of the risks of worsening hepatitis and frequent side effects.

Pregnant Woman: The nucleos(t)ides' are listed by the US Food and Drug Administration (FDA) as pregnancy category C drugs (lamivudine, adefovir, and entecavir) and category B drugs (telbivudine and tenofovir). There is a considerable amount of safety data on pregnant HIV-positive women who have received tenofovir, lamivudine, and/or emtricitabine.[36] In these women; tenofovir is preferred because it has a better resistance profile and more extensive safety data when usedduring pregnancy.[34,37]

Treatment in Immune Tolerant Phase: Most of the authors not recommend any treatment in immune tolerant Phase. But some studies recommend to start therapy with lamivudine alone for initial 8 weeks than both lamivudine and interferon for next 44 weeks to break the chain of long immune tolerant phase especially in vertically transmitted cases.[38,39]

HBV–HCV co-infection: In case of co-infection of HBV and HCV, HCV infection is to be treated first with 6 months course of interferon and ribavirin. Pegylated interferon was also found safe & effective in children.[30] If sero-conversion of HBeAgdo not occur after interferon therapy, long term treatment with lamivudine or adefovir can be started. [28]

HBV–HIV co-infection: Lamivudine &adefovir have got anti-HIV action. So lamivudine plus adefovir along with a third agent against HIV can be used.

Occult Hepatitis B Infection(OBI): It is the state of OBI needs no antiviral therapy usually. Antiviral drug should be started to OBI if chemotherapy or immunosuppressive therapy is to be given, especially in absence of anti HBs & continued up to 12 months after stoppage of immunosuppressive therapy.

Antiviral Resistance: We should suspect anti-viral resistance if there is inability to reduce HBV DNA 1 log10 IU/ml or more after 3 months of therapy, rise of HBV DNA at least 1 log10 IU/ml following treatment, rise of ALT following treatment and detection of gene mutation. To prevent anti-viral resistance we should initiate treatment only when indicated. Drug of optimal antiviral potency and low resistance should be used and sequential mono-therapy & interruption should be avoided.

Management of Drug Resistance:[34,38]

Lamivudine resistance	Adefovir resistance	Entecavir resistance
-Switch to tenofovir	- Switch to tenofovir	-Switch to tenofovir
-Add adefovir	- Switch to or add Entecavir	
	- Add lamivudinein the absence of previous lamivudine resistance	

Recommendations

1. All patients undergoing chemotherapy or treatment with other immunosuppressive therapies should be screened for HBsAg.
2. Patients testing positive for HBsAg should receive antiviral prophylaxis 2 weeks before starting treatment and continuing for at least 6 months after the last dose of immunosuppressive drug with close monitoring during and after therapy.
3. Patients with isolated anti-HBc who are immunosuppressed should have close HBV DNA monitoring and should be considered for antiviral therapy.
4. All pregnant women should be screened for HBsAg and, if positive, tested for HBV DNA, HBeAg, and ALT. Initiation of therapy should be in the third trimester.
5. HBV treatment should be considered in high-risk mothers to reduce the risk of vertical transmission in cases of high viral loads.
6. Patients should be monitored during pregnancy and postpartum for withdrawal flare-ups after nucleos(t)ide analog treatment is stopped.
7. The recommended first-line treatment during pregnancy is tenofovir (FDA category B).
8. Sequential mono-therapy & interruption should be avoided to overcome drug resistance.

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.[24] HBeAg 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.[26]

Prevention

HBV infection is such an illness that it is difficult to treat, outcome of treatment is guarded and morbidity & 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.[31] 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 2nd dose and 96% protection after 3rd 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.[41]

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.[42,43] Causes of failure of immune-prophylaxis (10-15%) are intra-uterine infection (5-10%), high

maternal viral load, genetic un-responsiveness, vaccine escape mutant and incomplete vaccination. Pre-vaccination screening is needed before vaccination. Blood for HBsAg, Anti-HBs or Anti-HBc total is sent for pre-vaccination screening. If any of the above markers is found positive, then no vaccination is needed. Following vaccination post vaccination test is to be done. Post vaccination of serologic testing of infant born to HBsAg +ve mother; should be ordered at age 9-12 months.[43] Anti-HBs titre is measured to see vaccine efficacy. Response is adequate if Anti-HBs titre is more than 10mIU/ml, 1-2 months after 3rd dose.[44]

Revaccination with further 1-3 doses induces protective anti-HBs response in the majority of nonresponders.[45,46] Immuno-compromised subjects should be tested annually and revaccinated if anti-HBs <10 mIU/ml.[47] Testing for celiac disease, HIV or other causes of immune deficiency might be advisable for non-responders.[48-50]

Recommendations

1. All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, followed by two or three doses of hepatitis B vaccines[51].
2. A routine booster dose of HBV vaccination is not indicated in immuno-competent individuals.
3. Repeating the vaccination is indicated if the first series of vaccination fails.
4. High risk individuals whose screening tests are negative for HBsAg and anti-HBs should receive hepatitis B vaccines.
5. Anti HBc (total) should be the test to screen blood donor, because HBsAg may be negative in window period and Anti HBS may be positive in sub-clinically infected person. Both the group can't give any blood or blood products.
6. Hepatitis A vaccine should be administered to all individuals with chronic liver disease.
7. A liver biopsy should be considered if the disease severity is unclear or if there is a possibility of coexisting liver disease.
8. All infants born to HBsAg-positive women should receive both anti-HBs immunoglobulin (HBIG) and HBV vaccines within 12 hours of birth.

Post exposure prophylaxis

Post exposure prophylaxis (e.g. Needle stick injury) is indicated after percutaneous or mucous membrane exposure to blood known or suspected to be HBsAg positive. Blood should be sent for HBsAg status of source & Anti- HBs of exposed person immediately. If source patient is HBsAg positive & exposed person has Anti HBs less than 10mIU/ ml & not vaccinated, HBIg plus vaccine (0, 1, 6 schedule) should started preferably within 24 hours. If source patient is HBsAg positive& exposed person has Anti HBs >10mIU/ml & no treatment is needed. Some experts consider one booster dose of vaccine. If source patient is HBsAg negative& exposed person has Anti HBs <10mIU/ml, initiate HB vaccine series (0, 1, 6 schedule)[45].

Health education about the transmission and the prevention of disease is the practical approach to safeguard our future generation. Routine screening of blood donors for HBsAg is mandatory.

Precaution should be taken when handling human blood and body fluid. Aseptic precaution should be taken during surgery, dental procedure and parenteral medication[41].

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.

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