

Recommendations for the Treatment of Chronic Hepatitis B infection in children

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Hepatitis B infection is endemic in our region and is associated with significant morbidity and mortality. These guidelines have been prepared to help physicians in our country in the diagnosis and management of Pediatric HBV infection.

It is estimated that greater than 350 million people worldwide have Hepatitis B infection. In Pakistan, there are estimated to be 4.5 million carriers of HBV with a carrier rate of 3-4%.¹

Mode of transmission

Hepatitis B is transmitted perinatally from mother to the baby, through contaminated body fluids, amongst families by horizontal transmission and also by the use of unscreened blood and blood products. It is also transmitted via the use of contaminated needles, surgical and dental equipment.

Children who need to be tested for HBV

Children at high risk of HBV infection include those, residing in high endemic regions of Pakistan, with a past history of blood transfusions and surgical procedures, born to mothers with HBV and with family members with HBV. Children with evidence of chronic liver disease need to be tested for HBV. The initial screening tests of choice are those for Hepatitis B surface antigen and antibody. Children who are seronegative require vaccination against HBV while seropositive patients require further evaluation.

Initial Evaluation of patients positive for HBsAg

Children positive for HBsAg require evaluation for chronic HBV infection. A good history and physical examination is required with particular emphasis on past history of jaundice, surgeries, blood transfusions and exposure to individuals with HBV. It is important to enquire about a family history of chronic liver disease or hepatic cancer. Laboratory investigations include serology for HBV as well as tests for co-infections with HCV and HDV. Quantitative HBV DNA assays are useful for management when available and a value of greater than 10⁵ copies per ml as has been used as diagnostic for chronic HBV infection (Table 1).

A liver biopsy may be indicated if treatment is being contemplated. The purpose of a liver biopsy is to assess the degree of hepatic damage as well as to evaluate for other pathology. The histological findings may also help in pre-

dicting prognosis.

Patients who are not considered for treatment on initial assessment

Patients who are positive for HBeAg with elevated serum HBV DNA and normal transaminases should be monitored every 3-6 months. More frequent monitoring may be required if the transaminase values remain elevated during this follow up period. Patients who remain positive for HBeAg with elevated HBV DNA should also be considered for further evaluation and treatment (Table 2).

Follow up of inactive HBsAg carriers

Patients with negative HBeAg and positive HBeAb are considered as inactive carriers for HBsAg. It is recommended that these patients are monitored every 6-12 months with tests for SGPT/ALT. Further work up is required for persistently elevated liver enzymes. This is recommended as in almost 30% of these patients reactivation of HBV may occur even after a prolonged period.^{2,3}

Prevention of HBV

Family members of patients with HBV infection should be vaccinated against the virus. HBsAg positive pregnant women should be counseled to inform their health care providers so that HBIG and HBV vaccine are given to the newborn immediately on delivery. The infants need to complete the vaccination series and should be followed for HBsAg and anti-HBs at 9-15 months of age. Infants protected with the vaccine and HBIG can be breast fed. Carriers should cover open cuts and clean blood spills with bleach as HBV can survive on environmental surfaces for a week.

Treatment of chronic Hepatitis B

The goal of treatment is to achieve sustained suppression of HBV replication and remission of liver disease. The end points of treatment include normalization of liver enzymes, undetectable HBV DNA, loss of HBeAg with or without emergence of HBeAb, and improvement in liver histology.⁴ The drugs that have been used to treat chronic HBV include Interferon, Lamivudine and Adefovir.

All patients with chronic HBV should be protected by vaccination against Hepatitis A.

Who to treat?

A sustained elevation of the ALT 2X normal for a period of 6 months in a child with HBeAg positive chronic hepatitis B indicates the need for treatment (Table 3). The end point of treatment is the conversion of HBeAg to the antibody.

Table 1. Evaluation for chronic hepatitis B infection.

Initial evaluation

1. History and physical examination
2. Laboratory tests to assess liver disease - complete blood counts, liver profile and prothrombin time.
3. Tests for HBV replication - HBeAg/anti-HBe, HBV DNA
4. Tests to rule out other causes of liver disease - anti-HCV, anti-HDV
5. Ultrasound examination of the liver and spleen.
6. Liver biopsy to grade and stage liver disease - for patients who meet criteria for chronic hepatitis.

Interferon, Lamivudine and Adefovir may be used for treatment. Adefovir use in children is still under investigation.

HBeAg negative patients with sustained elevation of transaminases 2x normal may be considered for therapy. The end point of treatment for these patients is the absence of HBV on PCR assay.

Compensated cirrhosis with HBV DNA positive may be treated with Lamivudine. PCR negative patients with compensated cirrhosis should be observed.

Antiviral treatment for inactive HBsAg carrier state ULN-uppre limit of normal is not indicated. These patients need to be followed every 6-12 months with serum transaminases and further work up for HBV DNA is required for elevation of ALT >1-2X normal (Table 2,3).

Table 2. Follow-up of patients not treated for HBV.

Suggested follow-up for patients not considered for treatment

HBeAg+ chronic hepatitis with HBV DNA >10⁵ copies/ml and normal ALT

- * ALT q 3-6 months
- * If ALT >1-2 x ULN, recheck ALT q1-3 months
- * If ALT >2 x ULN for 3-6 months and HBeAg+, HBV DNA >10⁵ copies/ml, consider liver biopsy and treatment

Inactive HBsAg carrier state

- * ALT q 6-12 months
- * If ALT >1-2 x ULN, check serum HBV DNA level and exclude other causes of liver disease

Co-infection with HBV and HDV

In most countries the only approved treatment for HDV is interferon alfa. The paediatric sequence of events does not follow adult pattern. Nucleoside analogues have not been effective in paediatric HDV infection. The primary

end point of treatment is reduced replication of the virus and improved transaminases. High dose IFN at 9 MU thrice a week for a year has been associated with beneficial effects in adult studies.⁵ Lamivudine has been found to be ineffective in the treatment of HDV.

Anti-viral prophylaxis in carriers who receive immunosuppressive or cancer chemotherapy

HBsAg testing should be done prior to initiation of chemotherapy. Prophylactic treatment with LAM is recommended for carriers at the onset of chemotherapy and maintained for 6 months after completion of the chemotherapy.⁴

Drugs used in the treatment of Hepatitis B

Interferon: Interferon alpha has been shown to have antiviral and anti-proliferative activity against HBV. The efficacy in children is similar to that in adults. Some patients may fail to respond to IFN and are called non-responders.

High pretreatment ALT and lower values of serum HBV DNA are the most important predictors of response to IFN therapy.⁶

1. HBeAg positive chronic Hepatitis B.

Interferon has been frequently used for the treatment of HBeAg positive patients. A 30% clearance of HBeAg has been reported amongst IFN treated patients as compared to controls in children with elevated transaminases. However fewer than 10% of those children with normal transaminases cleared the HBeAg when treated with interferon alpha.⁷

2. HBeAg negative chronic Hepatitis B

Optimal Treatment of HBeAg negative patients in paediatrics is still being debated and research is underway to establish the best possible way to ensure appropriate treatment. We are advocating currently following guidelines which protect the child from unnecessary extended interferon/lamivudine therapy. In these patients response to IFN therapy is determined by undetectable HBV DNA by un-amplified assays and a normalization of serum transaminases. Quantitative HBV DNA PCR would be helpful in following treatment response. Relapse after LAM monotherapy and resistance to LAM is high, with the recommended combination therapy time period for Lam may be extended to 2-4 years, the optimum time limit is not known however interferon is recommended for 6 months. Results of various studies have demonstrated an end of treatment response rate of 38-90% and a sustained response rate at one year of 10-47%.⁸ There is a high relapse rate with more than half relapsing with discontinuation of therapy. Relapses may occur up to 5 years after therapy and an improved response rate has been shown with a longer period of treatment of up to 24 months.⁹

Table 3. Treatment of chronic hepatitis B.

| HBV | | ALT | Treatment |
|-------|-------------------|-----------|--|
| HBeAg | DNA>105 copies/ml | | |
| + | + | >2x ULN | IFN 16 weeks LAM minimum of 1 year continued 3-6 months after seroconversion Contraindications to IFN use: use LAM End point of treatment conversion of HBeAg to antibody |
| - | + | >2x ULN | IFN 1 year LAM> 1 year End point of treatment is absence of HBV by PCR and sustained normalization of ALT |
| - | - | <2XULN | No treatment |
| +/- | + | Cirrhosis | Compensated cirrhosis: LAM Decompensated cirrhosis: refer for Liver transplant |
| +/- | - | Cirrhosis | Compensated cirrhosis: observe Decompensated cirrhosis: refer for Liver transplant |

3. HBV cirrhosis

IFN may induce a flare in patients with cirrhosis and should be used with extreme caution as it may precipitate hepatic decompensation.

Dose regimen

IFN is administered as a subcutaneous injection at a dose of 6 MU/m² thrice weekly with a maximum of 10 MU. Its use is associated with frequent side effects such as fever, fatigue, weight loss and leucopenia. The recommended duration of treatment for HBeAg positive chronic hepatitis B is 16-24 weeks. HBeAg negative patients should be treated for at least 12 months. An improved response rate has been seen with longer periods of treatment up to 24 months. The role of pegylated interferons in the treatment of hepatitis B in children is being evaluated.

While on IFN therapy, serial blood counts and liver profiles ought to be tested every 2-4 weeks.

Lamivudine (Epivir, 3TC)

Lamivudine is a nucleoside analogue that inhibits viral DNA synthesis. It has been shown to be safe and efficacious in children with chronic HBV.

1. HBeAg positive chronic HBV

HBeAg seroconversion rates were 22 % in treated patients versus 13% in controls. In addition, seroconversion is higher with elevated pretreatment transaminases.¹⁰ Lamivudine resistant mutants were identified in 19% of treated children during the 1 year treatment period.

2. HBeAg negative chronic hepatitis B and nonresponders

LAM has also been shown to be efficacious in the treatment of HBeAg negative chronic hepatitis B as well as in non

responders. Patients with failed IFN treatment show a similar response to LAM as treatment naive patients. Re treatment with IFN in addition to LAM provided no additional benefit to LAM monotherapy.

3. Cirrhosis

LAM is also well tolerated in patients with cirrhosis and results in clinical improvement in many patients.

LAM resistance

One of the problems associated with LAM treatment is the emergence of resistant mutants. The most common mutation affects the YMDD motif of HBV DNA polymerase. The resistance is manifested clinically as a breakthrough infection with a re emergence of HBV DNA after it was cleared from the circulation. Extended treatment is associated with increasing resistance. The clinical course in these patients is variable and long term effects are yet unknown. Most patients who do continue therapy have improved ALT levels and in 25% HBeAg seroconversion has been reported.¹¹

Dosage

The recommended dose for use in children is 3mg/kg/day with a maximum of 100 mg /day given orally. Dose reduction is required in renal compromised patients. The endpoint of treatment is seroconversion. Lamivudine therapy is administered for 1 year at least since shorter therapy is associated with poor rates of seroconversion. Treatment may be discontinued in those patients who have completed a year of therapy and have persistent HBeAg seroconversion (and absent HBV by PCR where possible) on more than one occasion 2-3 months apart.

Post treatment relapse is reduced if therapy is continued for an additional 3-6 months after seroconversion. Treatment may be continued in those patients who have not yet seroconverted. HBV DNA monitoring by PCR should be done if possible. For patients with the development of resistant mutants, therapy may be continued as long as the patient is improving or switched to adefovir. Adefovir use in children is being studied.

Discontinuation of LAM therapy may be associated with acute exacerbation of liver disease and may occur even a year post treatment. Hence all patients treated with LAM need to be monitored for a year after cessation of therapy.

It is unclear what the end point of treatment should be for HBeAg negative patients with LAM treatment, since relapses may occur even in those patients who seem to have cleared HBV by PCR. The recommended treatment duration is longer than 1 year but the optimal duration has not been defined.

Other drugs

Adefovir, entecavir, famciclovir and tenofovir are other anti-virals that are being studied.

The guidelines of ASLD were used in the preparation of this document.

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