Invited Review

Management of Chronic Hepatitis B in Children

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ABSTRACT

Hepatitis B virus (HBV) infection is a worldwide problem and can cause acute liver failure, acute hepatitis, chronic hepatitis, liver cirrhosis, and liver cancer. In areas of high prevalence such as in Asia, Africa, southern Europe, and Latin America, the hepatitis B surface antigen positive rate ranges from 2% to 20%. In endemic areas, HBV infection occurs mainly during infancy and early childhood. Mother-to-infant transmission accounts for approximately half of the chronic HBV infections. In contrast to infection in adults, HBV infection during early childhood results in a much higher rate of persistent infection and long-term serious complications such as liver cirrhosis and HCC. Three phases of chronic hepatitis B have been identified: the immune-tolerant phase, the immune-active phase, and the inactive hepatitis B phase. These phases of infection are characterized by variations in viral replication, hepatic inflammation, spontaneous clearance, and response to antiviral therapy. The optimal goal of antiviral therapy for chronic HBV infection is to eradicate HBV and to prevent its related liver complications. However, due to the limited effect of available therapies in viral eradication, the goal of treatment is to reduce viral replication, to minimize liver injury, and to reduce infectivity. In this review the current recommendations for monitoring and treating chronic HBV infection in children are reviewed. *JPGN 48:399–404, 2009.* **Key Words:** Chronic hepatitis B virus—Pediatrics—Viral hepatitis. © 2009 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Hepatitis B virus (HBV) infection is a worldwide health problem, which can cause acute liver failure, acute hepatitis, chronic hepatitis, liver cirrhosis, and liver cancer. It is most prevalent in Asia, Africa, southern Europe, and Latin America, where the hepatitis B surface antigen (HBsAg) positive rate in the general population ranges from 2% to 20%. Approximately 2 billion people in the world have been infected by HBV and more than 350 million are chronic HBsAg carriers.

In endemic areas, HBV infection occurs mainly during infancy and early childhood. Mother-to-infant transmission accounts for approximately half of the chronic HBV infections. In contrast to infection in adults, HBV infection during early childhood results in a much higher rate of persistent infection and long-term serious sequelae such as liver cirrhosis and hepatocellular carcinoma (HCC).

Three phases of chronic hepatitis B have been identified: the immune-tolerant phase, the immune-active phase, and the inactive hepatitis B phase. Most children with chronic HBV infection are immune tolerant, with high viral replication, positive hepatitis B envelope antigen (HBeAg), high HBV deoxyribonucleic acid (DNA) levels, and normal levels of aminotransferases (1,2). This pattern is mainly seen in children infected at birth. The immune-tolerant phase may last long into adulthood;

however, some of the infected children go into the immune-active phase. This phase is marked by active inflammation and elevated aminotransferases and may develop into fibrosis over time (3).

Most individuals with a sudden elevation of aminotransferases undergo spontaneous HBeAg/anti-HBe seroconversion. After HBeAg clearance, aminotransferase levels gradually return to normal limits, with anti-HBe developing spontaneously. The majority of individuals who demonstrate this clearance enter an ''inactive carrier'' state with normalization of aminotransferases, a reduction in HBV DNA levels, and improvement in hepatic inflammation (4). A fraction of patients retain hepatic inflammation with elevated aminotransferases and HBV DNA and remain in the immune-active state. There is a greater risk in the latter for the development of cirrhosis and HCC (4). A long-term follow-up study revealed a favorable overall prognosis for chronic hepatitis B in horizontally infected White children, yet 2% progressed to HCC and 6% had HBeAg-negative hepatitis (5).

Risk factors that have been associated with progressive hepatic inflammation and subsequent complications include the HBV genotype, persistent viremia, and specific mutations in the HBV genome.

The optimal goal of antiviral therapy for chronic HBV infection is to eradicate HBV and to prevent its related liver complication by shortening the duration of liver inflammation. However, due to the limited effect of available therapies in viral eradication, the goal of current antiviral therapy for hepatitis B is to

1. Reduce viral replication
2. Minimize the liver injury and related consequences in children with active viral replication and elevated levels of aminotransferases
3. Reduce infectivity

In this review, the current recommendations for monitoring children chronically infected with HBV and the considerations in and options for treating these children are reviewed.

MONITORING CHILDREN CHRONICALLY INFECTED WITH HBV

The natural history of the disease with HBV in children is complex and long-term data are still limited (5,6). As a result, defining the appropriate guidelines for monitoring and management has been difficult.

The most recent recommendations by the American Association for the Study of Liver Diseases (AASLD) (6) for monitoring HBV infections in adults were published in 2007. In this document it is recommended that all patients with persistently normal alanine aminotransferase (ALT) should have this liver enzyme monitored every 3 to 6 months. For those who are HBeAg negative

with a HBV DNA <2000 IU/mL, the ALT monitoring should be initially every 3 months but then can be lessoned to every 6 to 12 months. In those who are HBeAg positive, the persistence of this HBeAg positivity should be monitored every 6 months and the HBV DNA should be evaluated if the ALT becomes elevated. Patients with a persistently elevated ALT should undergo monitoring at least every 3 months, and for an ALT >2× the upper limits of normal (ULN) and HBV DNA ≥20,000 IU/mL, patients should be considered for treatment.

The best tool for the evaluation of the histological health of the liver remains the liver biopsy. Liver biopsy is not considered mandatory for treatment, but may be recommended to assess the necro-inflammatory grade/fibrotic stage and to exclude other etiologies of elevated ALT levels.

HCC is a potential risk of HBV especially in patients with advanced fibrosis or a family history of hepatic cancer. Although HCC has been reported in children with chronic HBV infection (7–9), the incidence is relatively low. As a consequence recommendations for screening pediatric patients have been slow to be developed, and most hepatologists follow the recommendations for monitoring adults with the infection. Many clinicians obtain serum alpha-fetoproteins at 6-month intervals with annual abdominal ultrasounds for surveillance. Performing both serum alpha-fetoproteins levels and ultrasounds every 6 months in those with significant fibrosis is recommended. Much of this screening is, however, done with medico-legal concerns because there are no data that suggest that such screening is cost-effective or that it may alter the natural course of disease. In endemic areas of hepatitis D virus (HDV) infection, HDV screening should be conducted in children with chronic HBV infection.

INDICATIONS FOR TREATMENT

Consensus guidelines for the treatment of chronic HBV in children have not been established, and indications for antiviral therapy in adults with chronic HBV infection may not be applicable to children (10).

Theoretically, treatment should be given as early in life as possible to interrupt viral replication and prevent liver damage due to chronic infection. Before initiating the therapy, a thorough evaluation of the liver function, HBV replication status, including biochemical tests, complete blood counts, HBV markers (HBsAg and HBeAg), and/or HBV DNA levels of the patients is essential (Table 1). Detailed discussion with the parents and/or patients about the disease status, indication for therapy, therapeutic options, advantage, possible risk, and problems of the therapies is crucial for good compliance with therapy and follow-up.

TABLE 1. *Suggested intervals of monitoring for children with chronic HBV infection*

Serum HBeAg	ALT levels	Interval of monitoring, mo
P	Normal	6
N	Normal	6–12
P or N	Elevation (<2× ULN)	3
P or N	Elevation (≥2× ULN)	1–2

P = positive; N = negative.

The decision to treat and the type of treatment selected requires consideration of HBeAg positivity, elevation of HBV DNA, the degree of necro-inflammatory activity and fibrosis in the liver, the immunological activity as reflected in ALT elevation, the patient's treatment history, and tolerance to prior treatment as well as coexisting disease states.

Factors that are predictive of a positive response to interferon (IFN) or nucleoside analogues include high pretreatment levels of aminotransferase (>2× ULN), low pretreatment HBV DNA levels (<10^5 copies/mL or 20,000 IU/mL), late acquisition of HBV infection, and higher hepatocellular inflammation.

Available information suggests that patients with normal or minimally elevated ALT levels respond poorly to available antiviral drugs, such as IFN or lamivudine (11,12). It is not clear whether such patients should be treated (except in the context of a clinical trial) because they are less likely to respond to treatment. Therefore, currently no drug treatment is recommended for this group of patients.

Treatment should be considered if patients have persistently elevated ALT levels >2× ULN and evidence of active viral replication (HBeAg seropositive, and/or HBV DNA levels >10^5 copies/mL or 20,000 IU/mL in their serum) for more than 3 months.

Acute elevation of the liver enzymes with an ALT level >5× ULN may be followed by spontaneous HBeAg seroconversion. It is, therefore, reasonable to delay treatment for an observation period of at least 3 months if there is no concern about hepatic decompensation (Fig. 1). Currently, children with persistently normal or minimally elevated ALT (<2× ULN) should be treated only in the context of clinical trial.

In patients with signs of hepatic decompensation, it is advisable to start non-IFN-based treatment as early as possible. Oral therapy with lamivudine has been shown to improve liver function and reduce the need for transplantation in these patients (13). Careful and frequent monitoring for progression of encephalopathy, serum bilirubin, and prothrombin time is recommended. If liver transplantation is an option, referral to a transplant center is recommended.

TREATMENT OF CHILDREN WITH CHRONIC HBV INFECTION

The goals of treatment are to reduce the risk of morbidity and mortality from cirrhosis and HCC, and to eradicate replicative infection by clearance of HBeAg.

The choice of HBV therapy depends largely on patient and viral factors, availability of the therapy, and required monitoring for that therapy. End of treatment is usually defined according to the virological response (VR), which is the absence of HBeAg and undetectable HBV DNA. The medications that are Food and Drug Administration (FDA) approved for the treatment of children
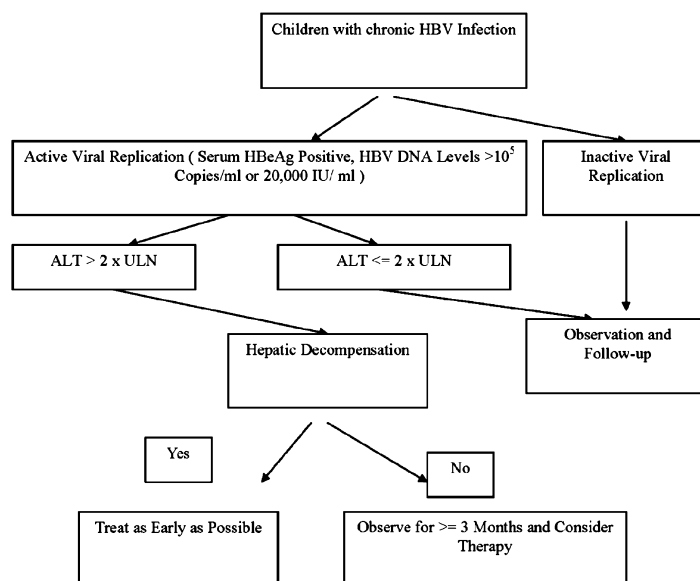

FIG. 1. Flowchart for the treatment decision making in children with chronic HBV infection.

with HBV include IFN-alpha, lamivudine, and most recently adefovir.

IFN-alpha is delivered by subcutaneous injection and was the first of the approved therapies for HBV. Predictors of IFN responsiveness include active hepatitis, low HBV DNA levels (<1000 pg/mL), high serum ALT (>2× ULN), short duration of disease, non-Asian ethnic origin, and horizontal transmission (14,15).

On the basis of European experience, consensus recommendations for the use of IFN-alpha for HBV-infected children, based on short-term efficacy, were developed. The main goals of therapy, according to these recommendations, are to accelerate HBeAg clearance in children with HBeAg and HBV DNA positivity, with low-intermediate HBV DNA levels and abnormal aminotransferase enzymes, ages 2 years or older (16).

IFN therapy is less likely to be of benefit in children with perinatally acquired infection who have normal or minimally elevated aminotransferase enzymes (17).

The recommended treatment regime for IFN-alpha is 5 to 10 million units per square meter thrice weekly by subcutaneous injection for 4 to 6 months. The response rates are variable, depending on route of acquisition, ethnic origin, disease activity, and treatment regime. Adult data suggest that HBeAg-negative chronic disease should be treated for 12 months, whereas another study demonstrates that longer durations of treatment of 24 months increased sustained response rates (18). Pretreatment with corticosteroids ("priming") and their withdrawal before commencing IFN-alpha may exacerbate the host immune response, facilitating seroconversion (19). The benefit, however, remains unproven (20), and is associated with the risk of precipitating fulminant liver failure.

A meta-analysis of 240 children in Europe demonstrated that IFN-alpha treatment increased both HBV DNA and HBeAg clearance (odds ratio 2.2) compared with untreated controls, although overall clearance of HBeAg clearance was only 23% compared with 10% of controls (21).

IFN is the only effective therapy for chronic hepatitis D, requiring high doses (9 million units for 12 months) with high relapse rates (22).

IFN is limited by its adverse side effect profile, although children tolerate treatment better than adults. Fever and "flu-like" symptoms are common when treatment is started, as is bone marrow suppression. Autoimmune thyroid disease, alopecia, and mental disturbance including severe depression are important side effects, but are rare in childhood. IFN-alpha is contraindicated in children with decompensated liver disease, cytopenia, severe renal or cardiac disorder, and autoimmune disease.

Pegylated IFN has not yet been approved by the FDA for the treatment of HBV in children, but in adults has shown benefits over IFN-alpha. The covalent attachment of a polyethylene glycol (PEG) moiety to IFN-alpha enhances its half-life and removes its immunogenicity, leading to once-weekly rather than thrice-weekly injections.

In adults the combination of PEG-IFN (180 μg/week) and lamivudine 100 mg daily for 48 weeks produced greater viral suppression, but no real difference in sero-conversion rates (23). There are a few small studies to date of pegylated IFN in children with HBV with or without lamivudine, but the results are inconclusive.

In view of the convenience of administration and similar side-effect profile, future studies of treatment are likely to be based on PEG-IFN.

Lamivudine is an orally administered pyrimidine nucleoside analogue. It prevents replication of HBV in infected hepatocytes, is incorporated into viral DNA leading to chain termination, and competitively inhibits viral reverse transcriptase. It leads to a rapid reduction in plasma HBV DNA load, with 97% reduction within 2 weeks of commencing treatment, and undetectable levels within 4 weeks, which is sustained during treatment (24). The AASLD has defined categories of response to antiviral therapy (Table 2). These categories have useful application to children as well.

TABLE 2. *Definition of response to antiviral therapy of chronic hepatitis B (6)*

Category of response	
BR	Decrease in ALT to normal level
VR	Loss of HBeAg and undetectable HBV DNA levels
Primary nonresponse	(not applicable to interferon therapy)
	No decrease in serum HBV DNA by <2 log 10 IU/mL after at least 24 wk of therapy
Virological relapse	Increase in serum HBV DNA of 1 log 10 IU/mL after cessation of treatment in at least 2 tests more than 4 weeks apart
HR	Decrease in histology activity index by at least 2 points and no worsening of fibrosis score compared to pretreatment liver biopsy
CR	Fulfill criteria of BR, VR
Time of assessment	
On therapy	During therapy
Maintained	Throughout the course of treatment
End of treatment	At end of defined course of therapy
Off therapy	After ending treatment
Sustained (SR-6)	6 months after cessation of treatment
Sustained (SR-12)	12 months after cessation of treatment

ALT = alanine aminotransferase; BR = biochemical response; CR = complete response; HBeAg = hepatitis B envelope antigen; HBV = hepatitis B virus; HR = histological response; SR = sustained response; VR = virological response.

As with IFN-alpha, the main goal of lamivudine therapy is to accelerate HBeAg clearance in children with HBeAg and HBV DNA positivity, low-intermediate HBV DNA levels and abnormal aminotransferase enzymes, ages 2 years or older.

Lamivudine is well tolerated, with a dose of 3 mg/kg/day (maximum 100 mg) providing levels of exposure and trough concentrations similar to that in adults receiving 100 mg (25). A subsequent international, randomized double-blind placebo controlled trial of 286 children with chronic HBV showed a complete response (eAg clearance and undetectable HBV DNA after 52-week treatment) in 23% compared with 13% placebo (12). In those with ALT $>2\times$ ULN, response rates were 34% and 16%, respectively. An emergence of the tyrosine-methionine-aspartate-aspartate (YMDD) variant was seen in 18%.

The optimal length of time to achieve VR with lamivudine has not been defined. The durability of the VR following treatment has also not been extensively evaluated in children. Some studies recommend a duration of 36 months of treatment until VR is achieved, with or without seroconversion (26). Others suggest that the necessary duration of treatment with lamivudine seems to be at least 1 year, with recommendations to continue treatment for 6 months after HBeAg seroconversion (27). Long-term lamivudine treatment (>3 years) did not significantly increase seroconversion rates and there was a higher incidence of viral resistance (26). Lamivudine should be discontinued once YMDD mutants have emerged (26), especially in the setting of ongoing transaminases elevation.

HBeAg status, ALT levels, and HBV DNA are used to monitor therapy and to predict the emergence of mutants. Recent reports suggest that serum HBV ribonucleic acid levels may also be useful in monitoring patients on therapy with lamivudine (28).

The most significant limitation of lamivudine is the development of viral resistance with prolonged use. HBV may acquire resistance to lamivudine due to a specific HBV mutation (YMDD mutation) in the polymerase gene (15). Due to survival advantage of the wild type by more effective replication, the mutant virus may revert to wild type after lamivudine therapy is withdrawn and rebound to pretreatment levels.

Lamivudine is not recommended currently as first-line treatment because more effective therapy is under evaluation (see below), except for compassionate therapy or co-infection with HIV.

Patients co-infected with HBV and HIV and those with an organ transplant are best treated with lamivudine (29) because IFN may be poorly tolerated.

Lamivudine has also been used to treat HBV-associated membranoproliferative glomerulonephritis, a well-described but uncommon complication of chronic hepatitis B infection (30).

Combination of IFN-alpha and lamivudine has had limited testing in clinical trials in children. Sequential treatment with lamivudine at 3 mg/kg for 8 weeks followed by IFN-alpha 2b for 44 weeks has been used successfully in the treatment of immune-tolerant children with perinatal infection with HBV. Seventy-eight percent were negative for HBV DNA at the end of the 52 weeks of treatment and 22% had seroconverted HBeAg. These patients were studied for 36 months after cessation of treatment. Seventeen percent achieved sustained viral control, and no YMDD mutants were identified during the course of treatment (31).

Adefovir is a purine analogue that inhibits viral replication and may also augment natural killer cell activity and endogenous IFN activity. Furthermore, HBV strains resistant to lamivudine are susceptible to adefovir (32).

A recent randomized controlled trial was conducted, which revealed that adefovir is effective in 22% of children aged older than 6 years, which is similar to adults, and rather less effective in younger children with little difference in efficacy compared to placebo (33). Viral resistance did not occur in the study, but it is reported in adults in 1% at 1 year rising to 29% at 5 years while treated by combination therapy with lamivudine. There is increased resistance to adefovir in patients who were previously resistant to lamivudine. Like lamivudine, it would not be considered first-line therapy in young children unless for compassionate use.

EMERGING ANTIVIRAL DRUGS

Telbivudine is an L-nucleoside analogue, which is more effective than lamivudine (in adults 26% compared with 23%), but has a high rate of viral resistance compared with adefovir and is not recommended as monotherapy (34). There are no studies in children, but they are being considered. On the basis of studies in adults telbivudine has been approved by the FDA for children older than 16 years.

Tenofovir disoproxil fumarate is a nucleotide analogue similar to adefovir that was originally licensed for the treatment of HIV. In vitro studies demonstrated activity against HBV, and clinical studies suggest increased potency compared to adefovir (35). Studies in children are planned.

Entecavir, a carbocyclic analogue, inhibits HBV replication at 3 different steps: the priming of HBV DNA polymerase, reverse transcription, and synthesis of HBV-DNA. It is more potent than lamivudine in suppressing wild-type HBV, but it is less effective in adults with lamivudine resistance. Viral resistance is rare. Studies are under way in children (36). Based on studies in adults entecavir has been approved by the FDA for children older than 16 years.

SUMMARY

Our understanding of HBV infection in children has greatly improved over the last decade, as therapeutic options emerge. Children 2 to 17 years of age who are HBsAg seropositive for more than 6 months with persistent elevation of ALT levels $>2\times$ ULN and evidence of active viral replication (positive HBeAg, HBV DNA levels $>10^5$ copies/mL or 20,000 IU/mL in their serum) for more than 3 months should be considered for therapy. Treatment with IFN, or lamivudine in children older than 2 years should be considered, but the side effects of IFN and the emergence of viral mutants mean that neither is ideal except for compassionate use. Adefovir is not sufficiently effective in children, but has the advantage of less viral resistance. Future therapies may hold more promise for HBV-infected children.

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