Chronic Hepatitis B management in Children

Aathira Ravindranath

Affiliations: *Department of Pediatric Gastroenterology, Apollo BGS Hospitals, Mysore- 570023, Karnataka*
Address correspondence to:
Aathira Ravindranath MD, DM
Associate Consultant
Department of Pediatric Gastroenterology, Apollo BGS Hospitals, Mysore- 570023, Karnataka
Telephone*: +91-8527710993,* ***Email****:* aathira.r@gmail.com
Conflict of interest*: None* ***Word count: 2559***

Abstract

Abstract

Chronic hepatitis B in children is mostly due to mother-to child transmission and risk of chronicity is highest when exposed in early infancy. The infection passes through different phases depending upon the degree of activation of immune system and status of HBeAg. Accurate assessment of each phase requires measurement of HBeAg, HBV-DBA and ALT. Treatment is indicated in those who are in HBeAg positive or negative hepatitis, in those with cirrhosis and extra-hepatic manifestations. Peg IFN and nucleos(t)ide analogues (NA) are the mainstay of treatment. Peg IFN though has a finite duration of treatment has many side effects. NA therapy with high barrier against resistance have fewer side effects but duration of therapy should ideally be until loss of HBsAg as even after HBeAg seroconversion chances of seroreversal or HBeAg negative hepatitis are there. Children undergoing immunosuppression should be screened not only with HBsAg but also with AntiHBc and NA prophylaxis should be initiated in those cases with high risk of reactivation.

Introduction

India remains a region of intermediate endemicity as hepatitis B virus (HBV) prevalence is about 3% in the general population. Mother-to-child transmission accounts for almost 2/3 of all cases of chronic hepatitis B in children. The risk of chronicity after exposure to hepatitis B is 90% in the newborn, 30% in children < 5 years and 5% in adolescents. Though chronic hepatitis B is seemingly innocuous during childhood, risk of cirrhosis is 3 to 5% and risk of hepatocellular carcinoma (HCC) is 0.01 to 0.03% even before reaching adulthood. Additionally, all these children carry the burden of the disease into adulthood when the risk of cirrhosis is 2 to 3% annually and that of HCC in those with cirrhosis is 3 to 8% per year.[1] Therefore, understanding the dynamics of chronic hepatitis B in childhood is essential to decide preventive and therapeutic strategies.

Natural history of chronic hepatitis B

Natural history of chronic hepatitis B is described using the new nomenclature based on the HBeAg status, HBV DNA (Hepatitis B virus deoxyribonucleic acid) and alanine aminotransferase levels (ALT) as a marker of liver inflammation. These phases result from the dynamic interaction between the virus and host immune system. The duration and outcome of each phase depend on a number of factors, the most important being the age of acquisition of infection.

1. HBeAg-positive chronic HBV infection: This phase was previously referred to as the immune-tolerant phase owing to the dormancy of immune system against the virus, thus allowing uncontrolled replication of HBV. This phase is characterized by HBeAg positivity, very high HBV-DNA and normal ALT signifying minimal or no liver inflammation. Perinatally acquired HBV or transmission of HBV in the first 2 years of life will have a prolonged HBeAg-positive chronic HBV infection which may last for 1 to 4 decades. Transplacental transmission of HBeAg induces immune tolerance thus explaining establishment of infection without any inflammation. Though there is hardly any parenchymal inflammation there is continuous integration of HBV-DNA into the hepatocytes and formation of covalently closed circular (ccc) DNA which forms the transcription template. Because of the random insertion of viral DNA into the host genome, a fertile background for development of hepatocellular

carcinoma (HCC) is formed. Even without evident features of inflammation, 1.7 to 4.5% of children infected at birth have cirrhosis on liver biopsy.[7]

2. HBeAg-positive chronic hepatitis B: In this phase there is activation of the immune system against the virus and is characterized by elevation in ALT, fluctuating levels of HBV-DNA and HBeAg positivity. Liver histopathology will show varying degree of necroinflammation. This phase was termed as the immune-active phase previously. This phase of active hepatitis is akin to a double edged sword. Activated immune system can cause HBeAg seroconversion in 65 to 90% in the long run. However, repeated flares of inflammation lead to progression of fibrosis. In children, early seroconversion is a risk factor for developing HCC as the severe necroinflammation forms an ideal background for carcinogenesis.

3. HBeAg-negative chronic HBV infection: After seroconversion majority will enter the "inactive carrier phase" which is now termed HBeAg-negative chronic HBV infection. In this phase ALT levels are normal, HBV-DNA is usually < 2000IU/L and Anti HBe is positive. Necroinflammatory activity is low and risk of progression to cirrhosis is low. Once this phase is reached there is a 1 to 3% chance of HBsAg loss annually. However, some may develop chronic hepatitis and move on to the next phase.

4. HBeAg-negative chronic hepatitis B: This phase is typified by elevated ALT, negative HBeAg, positive Anti HBeAg and moderately high HBV-DNA. Liver biopsy would show changes of inflammation and fibrosis. These patients have mutations in the core and pre-core regions that prevent HBeAg expression and still allow replication. Though only 10% children with chronic hepatitis B are in this phase there can be disease progression and higher risk of HCC. Adult studies have shown that those who have quantitative HBsAg level >1000IU/L have higher chances of reactivation.

5. HBsAg-negative phase: This phase is characterized by HBsAg negativity, Anti-HBs may or may not be detectable, Anti-HBc positivity, normal ALT and undetectable HBV-DNA. This phase was previously referred to as "occult HBV" phase. If this phase occurs before development of cirrhosis there is hardly any risk of disease progression or HCC. Annual risk of HCC after spontaneous HBsAg clearance is 0.55%. However, persistence of cccDNA in the hepatocytes would lead to reactivation when exposed to immunosuppression.

The summary of diagnosing hepatitis B in different phases of infection is given in Table 1.

Treatment

The ultimate goal of treatment is eradication of hepatitis B virus which in turn will stall disease progression and HCC development. Nevertheless, this will remain a utopian goal with the available treatment options presently. HBsAg loss signifies intense suppression of viral replication and is a desirable goal as disease progression correlates with viral replication. HBeAg seroconversion is a less desirable end point as there still remains the risk of seroreversion and HBeAg-negative chronic hepatitis.

Indications for treatment

As per the European Association for Study of Liver (EASL) recommendations for adults with chronic hepatitis B, all patients with HBeAg positive or negative hepatitis ought to be treated. These patients classically have ALT > ULN, HBV-DNA > 2000IU/L and moderate necroinflammation on liver biopsy. Irrespective HBV-DNA level, all patients with cirrhosis (compensated or decompensated) should be treated. Patients with HBeAg positive or negative chronic HBV infection are not offered treatment unless they have extrahepatic manifestations, family history of HCC or cirrhosis or if they are more than 30 years of age. In children, a decision to treat should take into account the slow progression of the disease in children, risk of complications later and the side effects of prolonged treatment. As patients with lower transaminases have lower chances of achieving seroconversion, only when the ALT is elevated more than 1.5 times the upper limit treatment can be considered. ALT can remain elevated for 6 months during spontaneous seroconversion hence, it is prudent to wait for 6 months before embarking on treatment. The cut-off for HBV-DNA is well established in adults as 2000IU/ml but until robust data in pediatric patients is available it is best to use the same cut-off though in some studies 20000 IU/ml has been used. Liver histopathology showing at least moderate necroinflammation or fibrosis would have better response to antivirals. However, there are some studies that have shown benefit of treatment even in the HBeAg positive chronic hepatitis B infection in children.

Treatment options

The two classes of drugs approved for treatment of chronic hepatitis B in children are pegylated interferon (Peg IFN) and nucleos(t)ide analogues

(NA) which include lamivudine, adefovir, telbivudine and entecavir, tenofovir disoproxil fumarate. Tenofovir alafenamide is a newer analogue that is approved in adults but not yet in children. Peg IFN based therapy has an immunomodulatory role which enhances host immunity against the virus and also has anti-viral effect. The advantages of Peg IFN therapy is the finite duration (180ug/1.73m^2/week for 6 months) of therapy, high barrier against resistance, moderate HBeAg and HBsAg loss and low risk of relapse. Drawbacks of this treatment are the numerous adverse effects, need for subcutaneous injections and contraindication in decompensated cirrhosis. Commonly used NAs are lamivudine (3 mg/Kg OD[Maximum 100 mg/day], < 2 years of age), entecavir (> 2 years of age) and tenofovir (>12 years of age). Entecavir (0.015mg/kg/day) and tenofovir (300mg/day) have high barrier against development of resistance, have fewer side effects but HBeAg and HBsAg loss is slow, duration of therapy is not defined (ideally until HBsAg loss) and there is risk of relapse on cessation of therapy. After achieving HBeAg seroconversion and undetectable HBV-DNA, NAs should be continued for at least 12 months more to consolidate the treatment. In those who do not seroconvert or in those with HBeAg negative chronic hepatitis B therapy with NAs should be continued indefinitely. As most of the children are in HBeAg positive chronic HBV infection phase they do not fulfill the traditionally defined criteria for treatment. Nevertheless, they have very high HBV-DNA levels, are at risk HCC development and are a source of transmission. Thus, some authors treated children in this phase with lamivudine for 2 months followed by combination of lamivudine and conventional interferon for 10 months and showed HBeAg seroconversion in 22% and HBsAg loss in 17%. Similarly an Indian study showed HBeAg loss in 39% and HBsAg loss in 20%.[18] The results are contradictory in another study which showed that sequential therapy is of no benefit in the immune-tolerant phase. Another recent study that used Peg IFN and entecavir showed that only 3% achieved HBeAg loss. Thus, with presently available evidence treatment in the HBeAg positive chronic hepatitis B infection (immune-tolerant phase) cannot be recommended.

Liver transplantation

Children undergoing liver transplantation for decompensated liver disease due to chronic hepatitis B should receive NA and Hepatitis B immunoglobulin (HBIG) after transplantation which reduces the chances of graft infection to < 5%. If the patient is HBV-DNA negative at the time of transplantation HBIG can be discontinued but NA's to be continued. But if HBV-DNA is positive prolonged therapy with NA and HBIG would be required. If a child with any other cause of liver disease is undergoing liver transplantation from a donor who is positive for Anti-HBc IgG, lifelong NA should be continued to prevent reactivation with immunosuppression.

Children undergoing immunosuppression

All children ought to undergo screening with HBsAg, Anti-HBs and Anti-HBc IgG before commencement of immunosuppression.

HBsAg – negative, Anti-HBs – positive, Anti-HBc – negative: Can proceed with immunosuppression

HBsAg – negative, Anti-HBs – negative, Anti-HBc – negative: Reinforced vaccination

HBsAg – positive, Anti- HBs – negative, Anti-HBc – positive: Prophylaxis with NA has to be started and continued until 12 months after completing immunosuppression (18 months in case of rituximab based immunosuppression). It has to be discontinued only if the disease is in remission. During prophylaxis liver functions have to be monitored every 3 months and 12 months after discontinuation.

HBsAg – negative, Anti-Hbs – negative, Anti-HBc – positive: The decision to start NA prophylaxis would depend on the risk of reactivation which is based on the immunosuppressive regimen.

- High risk of reactivation (>10%): In those who receive rituximab or stem cell transplantation, NA prophylaxis has to be given and continued for 18 months after cessation of immunosuppression with monitoring for at least 12 months after prophylaxis withdrawal.
- Moderate (1 to 10%) or low risk (<1%): HBsAg and HBV-DNA monitoring has to be done every 1 to 3 months as there is risk of seroreversion. If HBV-DNA becomes detectable or HBsAg becomes positive NA therapy has to be initiated.

Conclusion

In children with chronic hepatitis B phase of the disease has to classified based on HBeAg, Anti-HBe, HBV-DNA and ALT levels with or without liver biopsy. Cases with HBeAg positive or negative hepatitis need to be treated with anti-virals. More studies are needed to justify therapy in the HBeAg positive chronic HBV infection (immune-tolerant) phase.

Table 1: Phases of infection in chronic hepatitis B

	HBeAg positive chronic infection (Immunetolerant)	HBeAg positive chronic hepatitis (Immuneactive)	HBeAg negative chronic infection (Inactive carrier)	HBeAg negative chronic hepatitis
HBeAg	Positive	Positive	Negative	Negative
HBV-DNA (Copies/ml)	>20000	2000-20000	<2000	>2000
ALT	Normal	>ULN	Normal	>ULN
Liver histopathology	Normal	Moderate to severe necroinflammation/fibrosis	Minimal activity	Moderate to severe necroinflammation/fibrosis
Treatment	No	Yes	No	Yes

HBV-DNA: Hepatitis B virus-deoxyribonucleicacid, ALT: alanine aminotransferase, ULN: upper limit of normal

1 Batham A, Narula D, Toteja T, Sreenivas V, Puliyel JM. Sytematic review and meta-analysis of prevalence of hepatitis B in India. Indian Pediatr. 2007;44:663–74.

2 Satapathy SK, Garg S, Chauhan R, et al. Profile of chronic hepatitis B virus in children in India: experience in 116 children. J Gastroenterol Hepatol 2006; 21: 1170-6.

3 McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985;151:599–603

4 Chang M, Hsu H, Hsu H, Ni Y, Chen J, Chen D. The significance of spontaneous hepatitis B e antigen seroconversion in childhood: with special emphasis on the clearance of hepatitis B e antigen before 3 years of age. Hepatology 1995;22:1387–1392.

5 Luo Z, Li L, Ruan B. Impact of the implementation of a vaccination strategy on hepatitis B virus infections in China over a 20-year period. Int J Infect Dis. 2012;16:e82–e88.

6 Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68:723-750.

7 Lucifora J, Protzer U. Attacking hepatitis B virus cccDNA–The holy grail to hepatitis B cure. J Hepatol 2016;64:S41–S48.

8 Iorio R, Giannattasio A, Cirillo F, D Alessandro L, Vegnente A. Long-term outcome in children with chronic hepatitis B: a 24-year observation period. Clin Infect Dis 2007;45:943–949.

9 Bortolotti F, Guido M, Bartolacci S, Cadrobbi P, Crivellaro C, Noventa F, et al.Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. Hepatology 2006;43:556–562.

10 Tseng YR, Wu JF, Ni YH, Chen HL, Chen CC, Wen WH, et al. Long-term effect of maternal HBeAg on delayed HBeAg seroconversion in offspring with chronic hepatitis B infection. Liver Int 2011;31:1373–1380.

11 Lampertico P, Agarwal K, Berg T, Buti M, Janssen HLA, Papatheodoridis G, Zoulim F, Tacke F. EASL 2017 Clinical Practice Guidelines on the management

of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398.

12 Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology 2002;35:1522–1527.

13 Tseng TC, Liu CJ, Yang HC, et al. Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus load. Hepatology 2013;57:441–450

14 Liu J, Yang HI, Lee MH, Lu SN, Jen CL, Batrla-Utermann R, et al. Spontaneous seroclearance of hepatitis B seromarkers and subsequent risk of hepatocellular carcinoma. Gut 2014;63:1648–1657.

15 European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398.

16 Sokal EM, Paganelli M, Wirth S, Socha P, Vajro P, Lacaille F, Kelly D, Mieli-Vergani G. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Hepatol. 2013;59(4):814-29.

17 Hom X, Little NR, Gardner SD, Jonas MM. Predictors of virologic response to lamivudine treatment in children with chronic hepatitis B infection. Pediatr Infect Dis J 2004;23:441–445

18 Poddar U, Yachha SK, Agarwal J, Krishnani N. Cure for immune-tolerant hepatitis B in children: is it an achievable target with sequential combo therapy with lamivudine and interferon? J Viral Hepat. 2013;20(5):311-6.

19 Lee HW, Lee HJ, Hwang JS, Sohn JH, Jang JY, Han KJ, et al. Lamivudine maintenance beyond one year after HBeAg seroconversion is a major factor for sustained virologic response in HBeAg-positive chronic hepatitis B. Hepatology 2010;51:415–421.

20 D'Antiga L, AwM, AtkinsM, Moorat A, Vergani D, Mieli-Vergani G. Combined lamivudine/interferon-alpha treatment in "immunotolerant" children perinatally infected with hepatitis B: a pilot study. J Pediatr. 2006;148:228–233

21 Lal BB, Sood V, Khanna R, Rawat D, Verma S, Alam S. Pegylated interferon-based sequential therapy for treatment of HBeAg reactive pediatric chronic hepatitis B-First study in children. Indian J Gastroenterol. 2018;37(4):326-334.

22 Rosenthal P, Ling SC, Belle SH, Murray KF, Rodriguez-Baez N, Schwarzenberg SJ et al. Combination of Entecavir/Peginterferon Alfa-2a in Children With Hepatitis B e Antigen-Positive Immune Tolerant Chronic Hepatitis B Virus Infection. Hepatology. 2019;69(6):2326-2337.

23 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 2016;64:433–485.

24 Cholongitas E,Tziomalos K, Pipili C. Management of patients with hepatitis B in special populations. World J Gastroenterol 2015;21:1738–1748.