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ORIGINAL ARTICLE

Natural history and clinical management of chronic hepatitis B virus infection in children

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Abstract Hepatitis B virus (HBV) infection may cause acute, fulminant, or chronic hepatitis, leading to liver cirrhosis or hepatocellular carcinoma. Despite the availability of effective vaccine, HBV infection during infancy or early childhood is common in areas of high endemicity. In these regions, mother-to-infant transmission accounts for approximately 50% of chronic infections. Although the natural history of HBV infection in adults is well characterized, little information is available in the literature regarding the natural history of HBV infection in children. Similar to infection in adults, chronic HBV infection in children can be divided into distinct phases: immune tolerant, immune clearance, and inactive carrier state. However, acute exacerbation, with reactivation of HBV replication and re-elevation of alanine aminotransferase levels after hepatitis B e antigen seroconversion, is relatively rare in children, in comparison to adults. Although several potent antiviral agents are now available for the treatment of chronic hepatitis B, experience with these agents in the pediatric setting is limited. To date, conventional interferon α and lamivudine are the only two antiviral agents approved to treat chronic hepatitis B in children. The rapid emergence of resistant HBV associated with long-term lamivudine therapy, as well as poor tolerability associated with conventional interferon α, are factors that should be considered before initiating antiviral therapy. This article reviews current knowledge regarding the natural history and treatment of chronic hepatitis B in children. Factors that affect the natural history of HBV infection in children are also reviewed.

Keywords Hepatitis B virus · Chronic hepatitis B · Hepatitis B e antigen · Children · Adolescents

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Introduction

Hepatitis B virus (HBV) infection is a leading cause of acute and chronic liver disease in children and adolescents worldwide [1]. In areas of high endemicity, where the carrier rate for hepatitis B surface antigen (HBsAg) can approach 15–20%, most primary HBV infection occurs during early childhood. Infection during childhood is associated with a high rate of persistent infection and with an increased risk for morbidity and mortality from cirrhosis, decompensated liver disease, and hepatocellular carcinoma (HCC) later on in life [2–5].

Treatment strategies for children with chronic hepatitis B have focused on inhibition of viral replication to prevent active liver damage and induce hepatitis B e antigen (HBeAg) seroconversion. However, initiation of antiviral therapy in children is challenging and often controversial, particularly in chronically infected children who have high serum HBV DNA levels and normal aminotransferase levels. Currently, only conventional interferon α and lamivudine are approved for the treatment of chronic hepatitis B in children, and their use is limited by poor tolerability and emergence of drug-resistant HBV, respectively.

This review highlights the current understanding of the natural history of chronic hepatitis B in children and discusses factors that affect disease progression. Strategies for the treatment of chronically infected children are also presented.

HBV transmission

HBV can be transmitted either perinatally or horizontally. In regions of hyperendemicity such as Asia and the Pacific Islands, perinatal transmission from highly infectious mothers to their neonates is a common route of HBV infection, accounting for up to 50% of HBsAg carriers [6]. The age at which HBV infection is acquired is an important factor affecting the outcome of the infection. The probability of becoming a chronic HBV carrier correlates with the age at infection and the efficiency of the immune system; this probability is highest in children who become infected within the first year of life, as they tend to become immune tolerant to the virus. In the absence of immunoprophylaxis, more than 90% of infants born to mothers positive for HBeAg and HBsAg will develop chronic HBV infection, as compared to 23% if the infection occurs at preschool age (Table 1) [6–9]. Although the precise mechanism for the development of chronicity remains unknown, the presence of a relatively high maternal viral load, along with the physiologic immaturity of the immune system in the small neonate, may contribute to the high rate of chronic disease associated with perinatal infection. Individuals who acquired infection as young adults have a lower rate of chronicity (3–10%) [10].

HBeAg is a small viral protein that can cross the placental barrier from the mother to the infant. Transplacental HBeAg may induce a specific unresponsiveness of helper T cells to HBeAg and hepatitis B core antigen (HBcAg) in neonates born to HBeAg-positive HBsAg-carrier mothers [11]. This may cause the high rate of chronic infection and the long duration of immune tolerant status to HBV in children of these mothers. Intrauterine infection occurs rarely, in <5% of the infants of HBeAg and HBsAg-positive mothers [12].

Natural course of chronic HBV infection in children

HBV infection in children may run an acute, self-limited course, or a fulminant course progressing to hepatic failure with a high mortality rate, or it may persist for more than 6 months and become a chronic infection. The majority of chronically infected children are asymptomatic, exhibiting normal or minimally abnormal aminotransfersase levels; however, progressive inflammatory changes can occur in liver histology [2]. The natural history of hepatitis B infection in children can be divided into distinct phases: the HBeAg-seropositive phase (immune tolerant), the HBeAg-seroconversion phase (immune clearance), and the HBeAg-negative phase (inactive carrier). A brief description of these phases follows.

Table 1 Age of infection and maternal HBV status as factors influencing the outcome of HBV infection in children

Age of infection	Rate of persistent infection
Perinatal period	
Mother HBeAg+, HBsAg+	>90%
Mother HBeAg−, HBsAg+	<5%, with risk of fulminant or acute hepatitis
Preschool age	23%
Young adults	2.7–10%

From Beasley et al. [6, 7, 10]

Initial HBeAg-seropositive (HBV highly replicative) phase

The initial phase of chronic HBV infection, referred to as the immune tolerant phase, is characterized by the presence of HBsAg, HBeAg, and high serum HBV DNA levels ($\geq 2.0 \times 10^5$ IU/mL, or 10^6 copies/mL) [13]. Children in this phase are usually asymptomatic, having normal, borderline, or mildly elevated alanine aminotransferase (ALT) levels; liver inflammation is minimal or normal on biopsy.

HBeAg-seroconversion (acute exacerbation) phase

Although spontaneous HBeAg seroconversion may occur in childhood, it rarely occurs before the age of 3. In most instances, this process occurs during adolescence and early adulthood. The HBeAg-seropositive rate in HBsAg carrier children under 15 years of age is 80–85%. In a long-term follow-up study of 415 HBsAg-carrier children (ages 0–15 years) prospectively followed for 7.1 ± 2.9 years, the annual HBeAg-seroconversion rate was 4–5% in children older than 3 years of age, and it was <2% in children under 3 years [14]. Children in the early stages of HBeAg seroconversion still remain asymptomatic, or they have mild, nonspecific symptoms such as general malaise and poor appetite. HBeAg seroconversion is accompanied by an elevation of ALT levels and a decline in HBV DNA levels; the peak ALT levels may fluctuate from below 100 IU/L to more than 1,000 IU/L, depending on the liver damage sustained during this process of viral-host interaction.

HBeAg seroconversion is affected by age and maternal HBsAg status [15–17]. Factors affecting the clearance of HBeAg were studied in 169 healthy children who were positive for HBeAg and HBsAg [8]. In this study, only 7 (9.7%) of the 72 carrier infants seroconverted before 3 years of age. The HBeAg-clearance rate was lower in the infants whose mothers were positive for HBsAg than in those whose mothers had no detectable HBsAg (14.3% vs. 35.3%). Additionally, higher HBeAg-seroconversion rates

have been reported in horizontally infected children than in those infected perinatally [16, 18]. In a prospective study involving 174 HBeAg-positive children who were followed for a mean duration of 4.5 years, spontaneous seroconversion rates were 24% in children who acquired HBV infection perinatally and 44% in those who acquired their infection through horizontal transmission [18]. Similar findings have been reported in a cohort of white children infected with HBV who were followed for 29 years [16].

Although HBeAg seroconversion is associated with a decreased risk for liver complications later in life, early HBeAg seroconversion before 3 years of age in conjunction with elevated ALT levels in children may not reflect a good prognostic sign [14, 19]. Early HBeAg seroconversion to HBe antibody (anti-HBe), in association with severe liver injury, has been shown to play an important role in the rapid development of HCC in children [3]. A study of the histologic and virologic characteristics of 51 Taiwanese children with HCC revealed that low rates of positivity for HBeAg (18%) and liver HBcAg, coupled with a high frequency of liver cirrhosis, were associated with the development of HCC in children. These findings were confirmed in a large prospective study of 426 Taiwanese children with chronic HBV infection, which found that early HBeAg seroconversion or the presence of cirrhosis, or both, was a risk factor for HCC [19].

Post HBeAg-seroconversion (low replicative) phase

The third phase of chronic HBV infection, the inactive HBsAg carrier state, is characterized by the absence of HBeAg, the presence of anti-HBe, persistently normal ALT levels, and low or undetectable serum HBV DNA levels ($<2.0 \times 10^3$ IU/mL, or 10^4 copies/mL) [13]. Children in this phase may have nonspecific or minimal fibrosis. In contrast to adults, acute exacerbation of hepatitis, characterized by reactivation of HBV replication and re-elevation of ALT due to selection of precore variant virus, is a relatively uncommon complication in children and adolescents after seroconversion to anti-HBe [13, 15, 16, 20, 21].

Spontaneous loss of HBsAg is rare among children with chronic hepatitis B (<1% per year), especially if they have been infected during the perinatal period and have mild histologic changes [22–24]. In a prospective study of 420 HBV-carrier children who were observed for 1–12 years (mean, 4.3 years), spontaneous loss of HBsAg occurred in 10 patients, for an average rate of 0.6% per year [22]. Factors favoring HBsAg clearance included the presence of anti-HBe, older age, and HBsAg-negative status in the mother. After the loss of HBsAg, anti-HBs levels were higher in the children born to chronically infected mothers than in those born to noninfected mothers. These findings are consistent with those reported in a cohort of Chinese children followed up for a similar period of time [23].

Liver histology in children with chronic HBV infection

Liver histology in HBeAg-positive children generally reveals mild-to-moderate inflammation, with minimal fibrosis [14, 25]. During the process of HBeAg seroconversion, liver lobular changes develop, including portal inflammation and various degrees of fibrosis, with or without piecemeal necrosis. Although not common, bridging hepatic necrosis may occur during acute exacerbation. Within 6 months after HBeAg seroconversion, the inflammation is less active, and, beyond 6 months, it becomes inactive, and thus, in most children, inflammation and fibrosis are mild to minimal.

Various degrees of histologic abnormality are observed in children with chronic hepatitis B, even in the absence of elevated transaminase activity [4, 14, 25]. These changes can begin early in life and may accumulate more liver damage with time even though aminotransferase level is not significantly raised. A study involved 41 asymptomatic children with chronic HBV infection and had acquired HBV perinatally from HBeAg-positive HBsAg-carrier mothers. They had normal or minimal elevation of ALT levels at 1–9 years of age. The histologic findings included chronic active hepatitis in 1 patient, chronic persistent hepatitis in 8 patients, minimal changes in 30 patients, and normal histology in 2 patients [26]. Another 35 liver biopsies were studied in children with active liver diseases in a study involving children with perinatally infected hepatitis B carriers who were followed for a median of 10.24 years, and 60% showed a mild degree of fibrosis, and 18% showed moderate-to-severe fibrosis, suggesting a degree of progression, even in childhood [24]. Severe and permanent liver damage in the early stages of infection can progress to liver cirrhosis and HCC during childhood [8, 15, 16]. The prevalence and the clinical features of liver cirrhosis associated with chronic HBV infection were assessed in a prospective study involving 292 HBsAg-carrier children showing evidence of elevated aminotransferase activity [2]. Liver cirrhosis was observed in 10 patients (3.4%) (100% boys; mean age, 4.0 ± 3.3 years) at study entry. HCC in children with chronic hepatitis B presents mainly in the anti-HBe-positive phase, and that permanent liver damage occurs prior to HBeAg seroconversion [17]. In Asia, mother-to-child transmission of HBV infection is an important risk factor for HCC development. This is evidenced by the very high rate of seropositivity for HBsAg in HCC children and their mothers [3, 27].

HBV genotypes

HBV has eight genotypes, designated as A to H. Different genotypes are distributed in different geographic areas. Chronic infection with virus of the different genotypes may have a correspondingly different clinical course and outcome. Genotypes B and C are prevalent in Asia, while genotypes A and D are more common in Europe, Africa, the Middle East, and India. Children with HBV genotype C have a slower HBeAg-seroconversion rate than do those with HBV genotype B [25]. In a study that examined the prevalence and clinical significance of HBV genotypes in German children with chronic hepatitis B, genotype D was associated with higher viral load than genotypes A, B, and C [28]. However in other studies, HBV genotypes had no effect on the viremia profiles [13].

In Africa, HBeAg seroconversion occurs early in childhood, and HBV DNA positive rate was low (4.9%) in HBsAg carriers [29, 30]. It is associated with HCC in older children and young adults. In Alaska natives, transmission of HBV is horizontal and HBeAg clearance was earlier among children in Southwest Alaska, where HBV genotypes A, B, D, and F are found. In contrast, HBV transmission is perinatal and with a slower HBeAg seroconversion rate in Northwest Alaska, where HBV genotype C is found [31, 32]. In Alaska, HCC is mainly associated with HBV genotype F in younger ages (mean age, 22.5 years), and often without cirrhosis or core promoter mutations; while other genotypes were associated with older ages (mean age, 60 years), more core promoter mutations, and cirrhosis [33].

Precore and core promoter mutants

HBV wild type is the dominant strain during the long-term course of chronic HBV infection during childhood. An important G to A mutation at nucleotide 1896 of the HBV precore gene may lead to a stop codon, which causes a failure of HBeAg production. Analysis of 80 HBV-carrier children, both before and after HBeAg seroconversion during long-term follow-up, showed a gradual increase in the proportion with the precore stop codon mutant, from 10% at early HBeAg-positive status to approximately 50% (39–52%) after HBeAg seroconversion [34]. Prior to HBeAg clearance, the precore stop codon mutant emerged and coexisted with the wild type in only 25% of children with chronic HBV infection. A remarkable proportion (46%) of children had no detectable precore stop codon mutant throughout the long-term follow-up course, even after HBeAg seroclearance. Those in whom the precore stop codon mutant emerged before HBeAg seroconversion during follow-up tended to have higher levels of ALT, suggesting more severe hepatic damage. In an age-matched, case-control study, the HBV core promoter nucleotide 1762/1764 mutation did not demonstrate a major role in HBeAg seroconversion in children with chronic HBV infection [35].

Core gene mutants

Mutations within the HBV core gene have also been reported in children with chronic hepatitis B [35–37]. The incidence of HBV core gene deletion mutants was reported in a study involving 365 children with chronic HBV infection who were followed for more than 10 years [37]. Core gene deletion mutations were found in 18 of the children (4.9%). Most children with core gene deletion mutants underwent HBeAg seroconversion. Core gene mutation is more frequently seen in children with HCC, and the pattern of mutation is different from that in chronically HBV-infected children [36]. Core gene mutations occurred most frequently at codons 21, 147, and 65 (16–29%) within the HBV core gene in children with chronic HBV infection, whereas mutations at codons 74, 87, and 159 were more common in children with HCC.

Treatment of chronic HBV infection in children

Children with chronic HBV infection may develop active liver inflammation at any age, accompanied by a variable degree of ALT elevation, which increases their risk for more severe liver complications later on in life. Current antiviral regimens, while not effective enough to eradicate HBV, particularly in children, can prevent the progression of liver damage. However, most children with chronic HBV infection are in an immune tolerant status, in which they have a high viral load and normal levels of aminotransferases. As a result, response to conventional antiviral therapy is poor in those with normal ALT levels. Currently available therapies for the treatment of chronic hepatitis B are listed in Table 2. Of these, only interferon-α, administered subcutaneously at a dose of 6 MU/m^2 three times per week for 6 months, and lamivudine, administered orally at a dose of 3 mg/kg/day for at least 12 months, are approved for the treatment of chronic hepatitis B in children. A discussion of the criteria for initiating therapy and experience with currently approved antiviral therapy in children follows.

Indication for antiviral therapy in children

Children and adolescents (2–17 years old) who are HBsAg seropositive for more than 6 months, and have

Table 2 Antiviral agents for hepatitis B therapy

Drug	Advantages	Disadvantages
Approved for use in children and adults		
Interferon-α	Well-defined duration of therapy	Pain and inconvenience on injection
	No drug resistance	Multiple doses/week
		Other side effects: flu-like symptoms, depression, and bone marrow suppression
Lamivudine	Oral use	High rate of resistant strains
	Low side effects	Unclear duration of therapy
Approved only for adults		
Pegylated interferon-α	Well-defined duration of therapy	Pain and inconvenience on injection
	Single dose/week	Other side effects: flu-like symptoms, depression, and bone marrow suppression
	No drug resistance	
Adefovir	Oral use	Nephrotoxicity
	Low side effects	Unclear duration of therapy
	Effective against lamivudine-resistant strains	Weaker potency
	Lower rate of resistant strains in lamivudine naïve patients	Slower onset of therapeutic effect
Entecavir	Oral use	Unclear duration of therapy
	Low side effects	
	Low rate of drug resistance in lamivudine-naïve patients	
Telbivudine	Oral use	Unclear duration of therapy
	Low side effects	Resistance mechanism similar to lamivudine but occurs at a lower rate

elevated aminotransferase levels and HBV DNA in their serum for more than 3 months, may be candidates for antiviral therapy. Children and adolescents whose HBV DNA levels are $>10^5$ copies/mL, and whose ALT values are >2 times the upper limits of normal, should be considered for treatment as HBeAg seroconversion occurs more frequently in children with ALT >2 times the upper limits of normal [38]. Careful patient selection is as important in treating younger patients as in adults. A period of observation for at least 6 months is recommended before the start of therapy [39]. It is best to select patients who are likely to have a prompt response to therapy, before the risk of viral resistance escalates. In comparison to untreated control, children treated with an antiviral agent had an additional HBeAg seroconversion rate of approximately <5% in those with normal ALT levels, around 5–10% in those with ALT between 1 and 2 times upper limit of normal, and 25% in those with ALT >5 times upper limit of normal.

For children at risk for hepatic decompensation, antiviral therapy with lamivudine should be given as early as possible. Patients should be monitored carefully for serum bilirubin levels and prothrombin time, weekly or biweekly.

Conventional interferon α

The efficacy of interferon α for the treatment of chronic hepatitis B in children has been demonstrated in clinical trials [40–47]. In these studies, interferon-α therapy produced rates of HBeAg seroconversion and normalization of aminotransferase levels of 20–40%. Factors that are predictive of a positive response to interferon include high pretreatment levels of aminotransferase, low pretreatment HBV DNA levels, late acquisition of HBV infection, and presence of hepatocellular inflammation.

The response to interferon α therapy given for 3 or 6 months was studied in 107 children with chronic hepatitis B and followed for a mean period of 69 months. Long-term effects in treated children compared with untreated children revealed a similar HBeAg clearance-rate, 60% in treated patients versus 65% in controls [48]. While randomized trials of interferon in children showed higher rates of HBeAg seroconversion than placebo during short-term follow-up, the long-term follow-up rates of HBeAg seroconversion did not differ in children with versus without therapy with interferon. Thus interferon may accelerate the clearance of HBeAg in children. In addition, the rate of HBsAg loss was higher

non-responders (25%) for the interferon responders than for (0%) [48].

A systematic meta-analysis has shown a significant benefit of interferon therapy for chronic HBV infection in children [49]. Advantages associated with interferon therapy are the defined duration of treatment and the lack of development of drug resistance. With children, pain after injection and transient growth suppression are the main detriments associated with interferon therapy. Other side effects of interferon such as fever, general malaise, leukopenia, depression, or hair loss are less remarkable in children than in adults.

Lamivudine

Lamivudine is a nucleoside analog that can be administered orally. Lamivudine is well absorbed from the gastrointestinal tract, having a mean absolute bioavailability of 80% in adults and 68% in infants and children [50]. The efficacy of lamivudine has been demonstrated in children with chronic hepatitis B [51, 52]. Lamivudine treatment for 1 year may induce HBeAg seroconversion and serum HBV DNA negativity in children with chronic hepatitis B and high serum ALT concentrations [51]. However, loss of HBsAg is rarely achieved after only 1 year of lamivudine therapy (2%).

A recent study of prolonged lamivudine therapy found that an additional 24 months of therapy did not benefit the children who failed to achieve full virologic response and ALT normalization after the first year therapy [52]. Virologic response was maintained during follow-up in most children who underwent seroconversion to anti-HBe during the first 1-year lamivudine trial. Among these children, at 24 months of follow-up after the end of 1 year of lamivudine therapy, persistently normal ALT levels were observed in 71%, and virologic response was observed in 87%. In children who had received placebo during the first year, 92% had normal ALT levels and a sustained virologic response at the end of the 24-month follow-up [52].

The main disadvantages associated with lamivudine therapy are the high rate of emergence of resistant strains (e.g., YMDD mutants) and the unclear duration of treatment (Table 2). The incidence of lamivudine-resistant HBV increases over time, resulting in lower response rates. Higher pretreatment ALT levels and liver histologic inflammation scores, and lower HBV DNA levels, predict a better treatment response. Mutants of the HBV polymerase gene at the reverse transcriptase region may develop after use of lamivudine for more than 9 months [53, 54]. In a multicenter study, at week 52 after therapy, YMDD mutation was detected in 19% of the patients in the lamivudine group but in none of the patients in the placebo group [46]. Long-term use of lamivudine after the emergence of the YMDD motif mutation may lead to acute exacerbation and subsequent HBV clearance [55]. Careful monitoring of serum HBV DNA titre every 3–6 months and signs of clinical or biochemical deterioration of liver function is mandatory in children treated with lamivudine. Genotypic testing to confirm the resistant strains is recommended, if HBV DNA levels rise more than 1 log above the baseline.

Discontinuation of lamivudine therapy should be considered if biochemical exacerbation develops during therapy. Treatment options thereafter are limited, as no other antiviral therapy is approved for children except conventional interferon-α. Effective therapy is needed for children who experience severe exacerbation and risk of decompensation during or after lamivudine therapy.

Combination therapy

Combination therapies using different doses and time schedules of interferon α and lamivudine have been investigated in several studies [56–64]. These studies mostly involved small numbers of patients and yielded controversial results. A recent study with a larger number of patients (177 children) investigated therapy using lamivudine in combination with interferon α-2a, given at 9 MU/m^2 for 6 months [56]. Lamivudine was continued for 6 months after seroconversion to anti-HBe or was stopped at 24 months in nonresponders. Complete response was achieved in 55.3% of patients who received simultaneous lamivudine and interferon therapy and in 27.6% of those who received lamivudine 2 months prior to starting interferon ($P < 0.01$) [56]. Anti-HBe seroconversion occurred at higher rates and earlier, and HBV DNA clearance was earlier, in the simultaneous-treatment group ($P < 0.05$). The rates of HBsAg clearance were 12.5% and 4.6% in the simultaneous-treatment and sequential-treatment groups, respectively, and the respective rates of anti-HBs seroconversion were 9.8% and 6.2% ($P > 0.05$). Combination use of lamivudine and interferon-α seems to yield a higher response rate and even viral clearance than monotherapy in children. Further randomized control trials are needed to confirm the efficacy of combination therapy in children.

Future directions

Although the number of available, effective antiviral agents for hepatitis B, such as pegylated interferon α, adefovir, entecavir, and telbivudine, have expanded over the last decade, the experience with these agents in children is limited. The clinical trial of adefovir in children has been

completed, and it is waiting for the approval to be used in children. Clinical trials using entecavir or telbivudine in children are under planning or being conducted. In addition, experience and safety data available for tenofovir disoproxil use in children with HIV infection revealed proximal renal tubule damage and await for further careful evaluation [65].

Other new promising drugs in the late stages of clinical development, such as clevudine, have not yet been studied in children. Pegylated interferon-α is a long-acting interferon that has been successfully used for treating chronic hepatitis C, and it has also been used for treating hepatitis B in adults. Its reduced frequency of injection (once per week) has an advantage over conventional interferon-α, particularly in children. Although the safety and efficacy of pegylated interferon have recently been reported in studies of children with hepatitis C [66–68], similar studies have not been conducted in the setting of chronic hepatitis B.

Conclusion

HBV infection in children remains a serious problem, particularly in areas of high endemicity. Severe liver damage, including bridging hepatic necrosis, liver cirrhosis, and even liver cancer, although rare, may occur in children chronically infected with HBV. Over their long life expectancy, children may accumulate liver injury with time that increases their risk for cirrhosis and HCC later in life. Antiviral therapy is effective in suppressing HBV viral replication and inducing HBeAg seroconversion in children in the immune clearance stage of infection. Unfortunately, current antiviral regimens are not effective enough to eradicate HBV, particularly in children who acquire HBV perinatally. Antiviral therapy with interferon α or lamivudine is indicated for children in the immune activation stage if natural HBeAg seroconversion is not observed after at least 6 months. However, the effectiveness of these agents is limited by poor tolerability (interferon) and development of antiviral resistance (lamivudine). Newer antiviral therapies are needed for children, preferably ones that are associated with high efficacy and fewer side effects and that involve a shorter duration of therapy. The most desirable agents for children would also incur a low rate of drug resistance and produce a durable effect, protecting them from the complication of HBV infection over their lifetime.

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