MEETING REPORT

Treatment of Children With Chronic Hepatitis B Virus Infection in the United States: Patient Selection and Therapeutic Options

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Chronic hepatitis B virus (HBV) infection in children presents a therapeutic challenge for the practitioner. Decisions regarding selection of patients who may benefit from treatment, appropriate timing of treatment, and the choice of antiviral therapy are complex and are compounded by the limited number of drugs that have been studied in children. An expert panel of nationally recognized pediatric liver specialists was convened by the Hepatitis B Foundation on August 11, 2009, to consider clinical practice relative to the therapeutic options available for children. A detailed account of these discussions is provided, and the opinions expressed are based on consensus of the experts, as well as on published evidence when available. The panel concludes that, at this time, there is no established benefit of treatment of children in the immune tolerant phase, and there is a very high risk of development of drug resistance. In addition, there is no indication for treatment of children in the inactive carrier state. For children in the immune active or reactivation phases, liver histology can help guide treatment decisions, and family history of liver disease, especially hepatocellular carcinoma, may argue for early treatment in some cases. Outside of clinical trials, interferon is the agent of choice in most cases. Nucleos(t)ide analogues are secondary therapies, and children who receive these agents require careful monitoring for development of resistance. There are a few situations when treatment is indicated regardless of HBV DNA or alanine aminotransferase levels. There is still much to be elucidated about the appropriate use of HBV therapy in children. Until more clinical data and therapeutic options are available, a conservative approach is warranted. (HEPATOLOGY 2010;000:000-000.)

There are several published national and international guidelines regarding the management of adults with chronic hepatitis B virus (HBV) infection,[1–4] but standards for the treatment of children are still evolving. The decision to treat involves numerous factors such as the age of the child, the severity of liver disease, medical cofactors, and family history of liver disease or liver cancer. In addition to determining whom to treat, and when and for how long they should be treated, a particular challenge for practitioners is the limited number of drugs that have been studied and labeled for use in children.

Previously, an expert panel of nationally recognized pediatric liver specialists convened by the Hepatitis B Foundation in November 2008 called for more consistent monitoring and referral of children chronically infected with HBV, emphasizing that any child with elevated serum alanine aminotransferase (ALT) levels and/or elevated alpha-fetoprotein (AFP) levels and/or a family history of liver disease or liver cancer should be

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IFN, interferon; PCR, polymerase chain reaction; ULN, upper limit of normal; peginterferon, peg-IFN.

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referred to a pediatric liver specialist.[5] The panel assembled for a second meeting on August 11, 2009, to review the status of clinical practice relative to the therapeutic options available for children, and to highlight gaps in knowledge and areas for future study. The following is based on consensus of expert opinion and published evidence when available.

Natural History of HBV Infection in Children

Because most infants born in the United States are now vaccinated against HBV, the incidence of acute infection has decreased dramatically.[6] Children at risk for HBV infection include those who were not vaccinated, had an inadequate response to perinatal treatment or vaccination, or were exposed prior to being vaccinated. Immigrants from endemic areas and infants who are born to HBV-infected mothers but do not receive immunoprophylaxis or vaccine in a timely fashion are at particular risk, as are infants born to mothers with HBV DNA levels >20 million IU/mL in whom immunoprophylaxis and/or immunization is not always effective.[7] Approximately 90% of children infected as infants, and 25%-50% of children who become infected after early infancy but before 5 years of age, will develop chronic infection.[8-10] Only 5%-10% of those who become infected with HBV as teens or adults progress to chronic infection.[9] Most adults with chronic HBV infection acquired the infection in infancy or early childhood. Although most children with chronic HBV infection are asymptomatic and severe liver disease during childhood is rare, they are at risk for developing serious complications later in life, including cirrhosis and hepatocellular carcinoma (HCC).

Chronic HBV infection, defined as seropositivity for hepatitis B surface antigen (HBsAg) for more than 6 months, is characterized by four immunologic phases of disease (Table 1).[11,12] Most children will remain in the immune tolerant phase until late childhood or adolescence. The rates of spontaneous hepatitis B e antigen (HBeAg) seroconversion (loss of HBeAg and development of anti-HBe) for vertically infected children is less than 2% per year for those under age 3, and 4%-5% per year in children older than 3 years.[13] Children infected horizontally (after the perinatal period), have much higher rates of spontaneous seroconversion; 70%-80% seroconvert from HBeAg-positive to anti-HBe over 20 years.[14-16]

Children who are in the immune active phase, with persistently abnormal ALT levels and histologic findings of liver inflammation and fibrosis, are usually asymptomatic. However, studies in adults suggest that a prolonged period of time in the immune active phase is associated with an increased risk of cirrhosis and HCC.[17-20] Routine, lifelong monitoring for progression of disease and potential opportunities to treat is critical.[5] In addition, all persons with chronic HBV infection are at risk for HCC, and should be followed using the American Association for the Study of Liver Diseases Practice Guideline on HCC.[21]

Goals of Treatment

The current goals of therapy are to suppress viral replication, reduce liver inflammation, and reverse liver fibrosis, and thereby protect the liver. Treatment is geared toward reducing viral load until serum HBV DNA levels become undetectable by a sensitive polymerase chain reaction (PCR) assay and, for patients who are HBeAg-positive, achieving durable HBeAg seroconversion. Another desirable endpoint is normalization of ALT level, indicative of improvement in liver histology. HBsAg seroconversion occurs in a minority of persons receiving treatment, but it is the ultimate therapeutic goal because the risk of HCC is reduced, although not necessarily eliminated.[22] The long-term clinical impact of early therapeutic HBeAg seroconversion on the risk of complications later in life is unknown. A prospective observational study in more

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Table 1. Phases of Chronic Hepatitis B Infection

Phase	Laboratory Results and Histology	Note
Immune tolerant	HBsAg and HBeAg detectable	Biopsy not generally indicated
	HBV DNA >20,000 IU/mL (>10^5 copies/mL)	Antiviral therapies are generally ineffective
	ALT normal	Risk of drug resistance if treated with nucleos(t)ide analogs
	Absent or minimal liver inflammation and fibrosis	Continued monitoring recommended
HBeAg+ immune active	HBsAg and HBeAg remain detectable	Most children still show no signs or symptoms of disease
	HBV DNA >20,000 IU/mL (>10^5 copies/mL)	Biopsy indicated
	ALT persistently elevated	Appropriate testing should be considered to rule out other liver diseases
	Liver inflammation and fibrosis can develop	Treatment should be considered
Inactive HBsAg "carrier"	HBsAg present	Age at seroconversion appears to be influenced by HBV genotype
	HBeAg undetectable, anti-HBe present	Risk of developing cirrhosis declines
	HBV DNA <2000 IU/mL (<10^4 copies/mL) or undetectable	Risk of developing HCC
	ALT normal	Biopsy generally not indicated
	Absent or minimal liver inflammation, fibrosis will regress over time	Continued monitoring recommended
Reactivation or HBeAg-negative immune active	HBsAg present	Occurs in 20-30% of patients
	HBeAg remains negative and anti-HBe positive	Called "e-antigen-negative" hepatitis B
	HBV DNA levels >2000 IU/mL (>10^4 copies/mL)	Usually due to basal core promoter or precore mutation
	ALT normal or elevated	Liver biopsy indicated, especially if ALT abnormal
	Active liver inflammation ± fibrosis	Treatment should be considered if moderate or severe inflammation or fibrosis present
		Treatment with nucleos(t)ide analogs may be long-term

than 400 children suggests that HBeAg seroconversion in children is not necessarily an indicator of good prognosis, citing development of HCC in children who were early spontaneous seroconverters.[23] Ultimately, the goal of any anti-HBV therapy is to reduce the risk of progressive liver disease, cirrhosis, and HCC.

Patient Selection for Treatment

Children identified as having chronic HBV infection require routine monitoring for progression of disease, including physical examinations, and laboratory assessment of ALT, AFP, HBeAg/anti-HBe status, and HBV DNA level.[5] In addition, a full liver panel and platelet count should be checked sporadically. Increasing ratio of aspartate aminotransferase (AST) over ALT is often a sign of increasing fibrosis, especially if AST value becomes greater than ALT,[24] although this has been more clearly demonstrated in chronic hepatitis C[25,26] than hepatitis B[27] and could be confounded in the rare instance of concomitant alcoholic liver disease. The possibility that a child with chronic HBV infection and AST > ALT has cirrhosis is significant enough to mandate further evaluation, possibly including liver biopsy. However, AST > ALT level can also be seen transiently in children recently consuming alcohol or after vigorous physical activity, and these possibilities need to be ruled out before undertaking a search for advanced fibrosis due to HBV. Thrombocytopenia may be an early sign of hypersplenism from portal hypertension. Children who develop signs of active hepatitis or those who have a family history of HBV-related liver disease, especially HCC, should be referred to a pediatric liver specialist for consultation and development of a management strategy.[5]

Although serum ALT level is a useful indicator of liver damage or disease, the definition of what is a normal or healthy ALT value has been the subject of much discussion. It has been suggested that the upper limits of normal (ULN) for men and women are 30 IU/L and 19 IU/L, respectively,[28] but the ULN for children has not been established. Adult guidelines can generally be applied to older adolescents. However, for younger children, the ULN used often varies according to the testing laboratory and the age of the child. In the absence of standards for children, the panel has previously recommended that, for purposes of HBV monitoring, a child's ALT should be considered elevated if it is greater than the testing laboratory ULN, or >40 IU/L, whichever is lower.[5] A detailed physical examination focusing on the size and character of the liver and spleen, as well as extrahepatic manifestations (including clubbing, spider angiomata, hypoxia, and/or cardiopulmonary findings) may uncover advanced liver disease and sequelae of cirrhosis and portal hypertension in those who may have normal or near normal ALT.

The panel's consensus approach to selection of children for HBV antiviral treatment is presented in

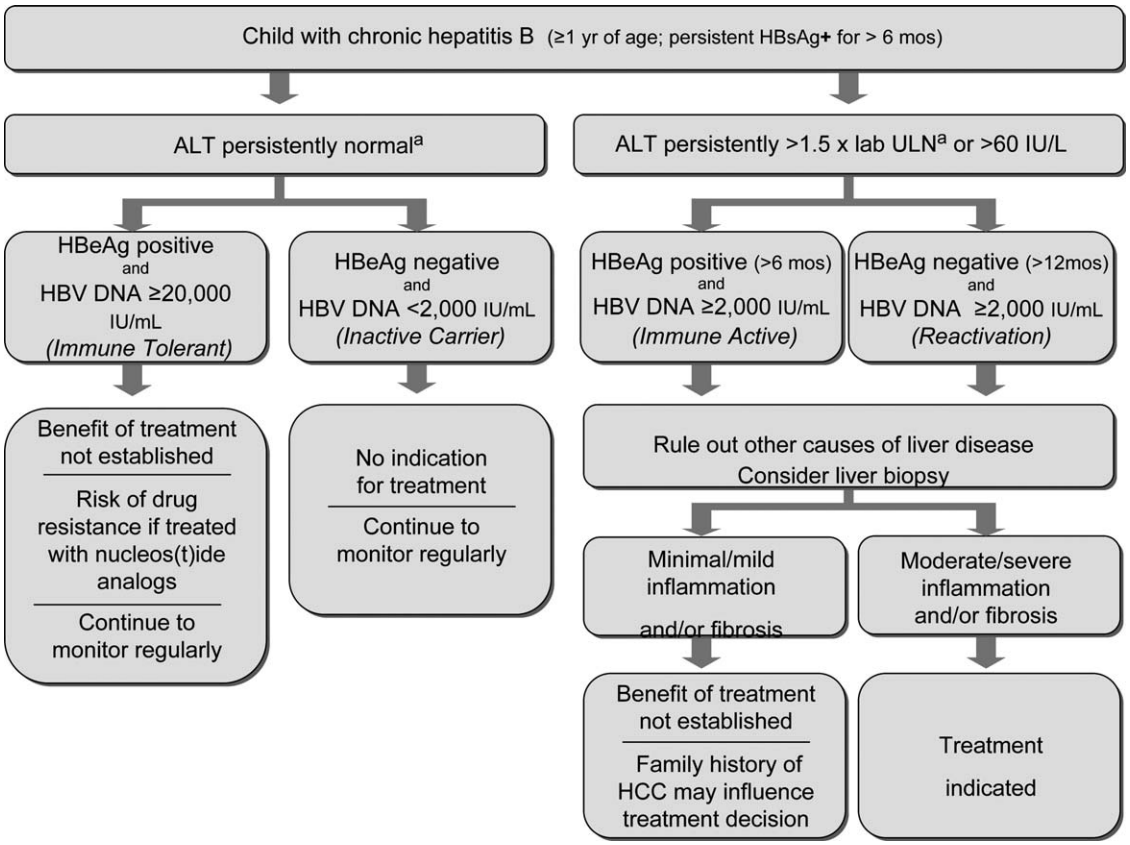

Fig. 1. Algorithm for selection of children for HBV antiviral treatment.

Fig. 1. Primary factors in the decision to treat are, sequentially: ALT level, HBV DNA level, and liver histology. There are also special populations in whom treatment should be considered regardless of ALT or HBV DNA levels (Table 2). Predicted patient adherence to the treatment regimen is also a factor in the decision to treat, because nonadherence to a regimen of nucleos(t)ide analogue can result in the development of resistance secondary to intermittent therapy. In such cases, nontreatment is preferable to noncompliance, in order to prevent the development of resistance associated with oral antiviral medications, and thus preserve treatment options for the future.

Children with Normal Serum ALT

In the management of children with chronic HBV infection, understanding which children should not be treated is as important as identifying those who should be treated. A primary consideration is the child's serum ALT level. Persistently normal ALT levels are characteristic of the immune tolerant phase and the inactive HBsAg carrier phase.

Immune Tolerant Phase. As discussed above, the majority of children who are infected perinatally remain in the immune tolerant phase for much of their childhood and often well into adulthood. The longest duration of the immune tolerant phase is typically seen in those infected with HBV genotype C, and rates of HBeAg seroconversion in children with genotype C are very low.[16] These children remain positive for HBeAg, with high HBV DNA levels, $\geq$ 20,000 IU/mL (equivalent to 10^5 copies/mL) and usually much higher. However, there is no immune response to cause active disease and ALT levels remain normal. Although some practitioners conclude that the high viral DNA levels in these children warrant treatment, the benefit of treatment with currently available agents in the immune tolerant phase has not been established. It may be detrimental in the long run due to the development of antiviral resistance at a time when liver disease is minimal.

Published clinical data supporting the treatment of children in the immune tolerant phase are very limited. One very small pilot study reported that combined lamivudine and interferon (IFN) alfa2b treatment reduced viral load in children with normal ALT and mild histologic changes.[29] Eleven of the 23 treated children had undetectable HBV DNA by PCR at the end of treatment. Five remained negative for HBV DNA at follow-up and had seroconverted to anti-HBe;

Table 2. Special Circumstances in Which Either Temporary or Long-Term Treatment of Children With Chronic HBV Infection Should be Strongly Considered

Rapid deterioration of liver synthetic function
Cirrhosis (compensated or decompensated)
Glomerulonephritis due to HBV infection
Prevention or treatment of recurrent HBV infection after liver transplantation
Recipient of a liver graft from an anti-hepatitis B core antigen (anti-HBc)-positive donor
Need for immunosuppression or chemotherapy
Presence of coinfections (HBV/HIV, HBV/HCV, HBV/HDV)
Children with a strong family history of HCC who are in the immune active phase
Pregnant females with high viral load (>20 million IU/mL) in the third trimester, especially those who have had a previous infant with failed perinatal immunoprophylaxis

four also achieved HBsAg seroconversion. Other studies in children defined as immune tolerant used nondrug interventions, such as therapeutic HBV vaccination[30] and vitamin E.[31] In the first study, no difference in rates of clearance of HBV DNA or HBeAg seroconversion was observed in children who received HBV vaccine as active immunotherapy compared to similar unvaccinated children. The second study demonstrated no observable beneficial effect of vitamin E.

In the short term, there is little indication that children in the immune tolerant phase will develop progressive liver disease during childhood. There is, however, substantial concern regarding the emergence of drug-resistant strains of the virus if nucleoside or nucleotide analogues are administered during this period.[32] Early infection does confer a risk of chronic hepatitis and HCC later in life; it is most prudent to monitor these children for immune activation, when therapies are more likely to be effective.

Young children who receive inappropriate or unnecessary treatment with nucleos(t)ide analogues, and subsequently develop drug-resistant infections, may find themselves at a therapeutic disadvantage 20-30 years later if, as adults, they develop complications such as cirrhosis, and their treatment options are then limited. It is the consensus of the panel that children in the immune tolerant phase not be treated under normal circumstances (outside of clinical trials). It is important that practitioners take the long view of the treatment of children with chronic HBV infection, and consider the ramifications of treatment of an asymptomatic child on the future adult who will be at higher risk for complications that may subsequently require treatment.

Inactive HBsAg Carrier Phase. Children in the inactive HBsAg "carrier" phase that follows HBeAg seroconversion, whether spontaneous or treatment-induced, have normal ALT levels, are HBeAg-negative, and have undetectable or low levels of HBV DNA (<2000 IU/mL, equivalent to $<10^4$ copies/mL). There is no indication for treatment of children in this phase. In addition, if these children were to be treated, there is no discernable endpoint because all values are already normal or undetectable and HBeAg is negative. However, because an estimated 20% of persons in the inactive carrier stage will subsequently have recurrent flares of hepatitis, revert to HBeAg-positive immune active hepatitis, or progress to the HBeAg-negative active hepatitis phase, all characterized by elevation of HBV DNA and ALT levels, patients in the inactive carrier phase need lifetime follow-up every 6-12 months with testing for ALT. Persistent elevation of ALT is an indication for further evaluation.[5]

Children with Persistently Elevated Serum ALT

Elevated serum ALT level is a useful indicator of liver damage or disease. Assuming that other causes of liver disease are excluded, children with persistently elevated ALT levels are in the immune active, or possibly, reactivation phases of disease. These children warrant further evaluation, including measurement of HBV DNA level and liver histology, to determine if treatment is appropriate.

ALT Level. Recent data demonstrate that current laboratory "normal" values for ALT in children may underestimate the prevalence of true abnormalities. Just how insensitive ALT is for identifying children at risk for clinically significant liver disease, including chronic hepatitis B, is unknown.[33] Pending verification and validation of these findings in more cohorts, the panel favors a somewhat conservative and global cutoff for ALT as indicative of liver damage and thus a possible indication for therapy. Specifically, to be considered for possible treatment, a child's ALT should be elevated more than 1.5 times the laboratory ULN, or more than 60 IU/L (i.e., 1.5 × 40 IU/L), whichever is lower, on at least two occasions over a minimum of 6 months for HBeAg-positive disease, and at least three times over 12 months for HBeAg-negative disease. The reason to monitor ALT for persistent elevation for at least 6 months in patients with HBeAg-positive disease is to avoid treating a child in the process of spontaneous HBeAg seroconversion, who will improve without treatment. The basis for using 1.5 × ULN is the ALT values used as inclusion criteria for the three largest prospective, randomized, controlled pediatric safety and efficacy trials of antiviral treatment in children.[34-36] However, there are no strong data to

support a specific ALT level as an indication for treatment. Whatever level is chosen increases the probability of a false positive for advanced disease if too low, and false negatives if too high. Consequently, liver biopsy may provide important information if treatment is contemplated. Evaluation for treatment in adults over 40 years of age may be recommended solely on the basis of HBV viral level, based on several prospective studies showing that high viral load in persons above age 40 is an independent risk factor for HCC and cirrhosis.[17,37-39] Treatment selection criteria developed for adults, however, may not be the most appropriate approach for selection of children for treatment. There are currently no data to implicate viral level, in and of itself, during chronic infection in childhood, on the development of sequelae later in life.

Some previous publications have suggested a cutoff of twice the ULN to indicate treatment in children with chronic HBV.[4,40] The panel prefers a slightly lower level for which to consider therapy, based on limited data regarding histologic abnormalities, the imprecise determination of normal ALT values in this population, and the criteria used in the large registration trials in children. The decision to treat is not made on ALT values alone, but includes factors such as age, liver biopsy findings, comorbidities such as obesity, and family history of HBV-associated cirrhosis or HCC. For example, in obese children, it is important to consider that ALT elevations may be due to fatty liver disease, and not to the HBV infection. Children with a family history of HBV-associated HCC may be treated even though liver disease is relatively mild.

HBV DNA. Children with persistently elevated ALT as described above should be assessed for evidence of active viral replication. Serum HBV DNA levels >2000 IU/mL merit further evaluation for treatment by consideration of liver histology and efforts to rule out other causes of liver disease. This value has been extrapolated from treatment guidelines for adult patients, but in the majority of pediatric cases viral levels are substantially higher (typically >20,000 IU/mL in the immune active phase, often >6 $\log_{10}$ IU/mL). Thus, at present, the absolute level of serum HBV DNA levels that warrants concern in children may be, with data from future studies, distinct from those currently recommended for adults.

Liver Histology. Liver biopsy is recommended in most children with compensated liver disease prior to therapy. Histologic findings from a liver biopsy are used to define the severity (grade) of inflammation and the stage of fibrosis, which in turn can help inform treatment decisions in a patient with persistently elevated ALT and evidence of viral replication. In general, demonstration of moderate to severe necroinflammation, and/or anything more than mild portal fibrosis, supports initiation of antiviral therapy. In contrast, the benefit of treatment has not been established for patients with minimal to mild necroinflammation and/or fibrosis. However, because a family history of HCC puts a child at a higher risk of developing HCC in the future, some experts consider such a family history as adequate cause to lower the histologic threshold for treatment.[41] Histologic findings can also help predict response to treatment and prognosis. However, there is interobserver variability in interpreting liver biopsies from HBV-infected children.[42] Greater degrees of histologic activity correlate with higher likelihood of response to treatment with both IFN-alfa[34] and nucleoside analogues.[43] For these reasons, it is the consensus of the panel that only those persons with moderate inflammation or at least moderate fibrosis should be considered for treatment.

Evaluation For Other Known Causes of Liver Disease. In patients with elevated ALT, practitioners should consider the possibility of other liver disorders and conduct testing as appropriate. For example, elevated ALT levels in obese children may be related to nonalcoholic fatty liver disease. Consideration of genetic/metabolic liver disease; autoimmune hepatitis; Wilson's disease; coinfection with hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV); heavy alcohol usage; or drug hepatotoxicity may be warranted, depending on the patient's history. The extent of evaluation for other causes of liver disease varies from patient to patient; children with HBV DNA levels below 2000 IU/mL generally require the most extensive evaluation. Unfortunately, comorbidities can confound treatment decisions. For example, it may not be possible to determine if inflammation or fibrosis observed on biopsy is due to active HBV infection or to nonalcoholic steatohepatitis in an overweight child with chronic HBV infection.

Special Populations That May Warrant Treatment

In addition to the identification of potential treatment candidates per the algorithm in Fig. 1, there are special populations in whom treatment of HBV infection should be considered, regardless of HBV DNA or ALT levels. These potential indications for treatment are outlined in Table 2. These children may experience rapid deterioration of liver function, acute liver failure,

Table 3. Differences in Age at Clearance of HBeAg by HBV Genotype Among Those Initially Positive for HBeAg[ab]

Genotype	Number of Patients	Age at Clearance (Years)		
		25th percentile	50th percentile	75th percentile
A	34	13.8	19.4	32.1
B	6	17.8	19.5	27.5
C*	36	19.3	47.8	58.1
D	305	10.8	18.0	27.3
F	126	10.6	16.1	24.5

*Patients infected with genotype C were older at time of HBeAg clearance than were those with other genotypes ($P < 0.001$). Reprinted with permission from Livingston et al.[16]

or decompensated cirrhosis, whether or not treatment is instituted.

For HBV-infected children about to receive immunosuppressive or cytotoxic chemotherapy, preemptive antiviral treatment is almost always indicated to prevent increased viral replication and consequent clinical deterioration. Studies have shown that, in adults, starting lamivudine before chemotherapy decreases the risk of hepatitic flare from 50% to 10%, and decreases the severity of flares that do occur.[44,45]

HBV Genotype

There are eight known genotypes (A through H), and several subtypes of HBV, which vary in predominance geographically.[46-48] Studies in adults suggest that the progression of liver disease may be influenced by genotype; for example, genotype C has been associated with an increased risk for HCC compared to genotype B.[49] Perinatal transmission of HBV may also be related to genotype. A prospective study of adults from the Alaska Native population found that the majority of cases of perinatal transmission were associated with genotype C.[16] In addition, those infected with genotype C were significantly older at HBeAg clearance (median age, 47.8 years) than those with genotypes A, B, D, or F (median age <20 years; Table 3). Similarly, studies conducted in Asia indicate that individuals infected with genotype B have earlier spontaneous HBsAg seroconversion than those with genotype C.[50]

Therapeutic response to antiviral drugs, particularly interferons, may also vary by genotype. Studies have shown, for example, that, in adults, HBV genotype A is more responsive to IFN therapy than genotype D, and genotype B is more responsive than genotype C.[51,52] At this time, however, definitive information on the relationship between HBV genotype and disease progression or therapeutic response is limited. Thus, in children, therapeutic decisions cannot be based primarily on genotype at present.

Therapeutic Options

In the United States, there are now seven drugs approved by the U.S. Food and Drug Administration for treatment of chronic hepatitis B in adults: two forms of interferon, IFN alfa-2b and peginterferon alfa-2a (peg-IFN), and five nucleos(t)ide analogues, lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate. Of these, four are labeled for use in children (individuals <18 years old). Lamivudine may be used starting at 3 years of age, adefovir is labeled for those aged 12 years and older, and entecavir for age 16 years and older. IFN-alfa is approved for use in children as young as 12 months of age. No antiviral drugs are approved for treatment of children under the age of 1 year. Treatment is not usually required in this age group.

Interferon-Alfa

IFN-alfa-2b has been used for the treatment of chronic HBV infection in children for more than a decade. Some experts, including members of this panel, regard it as the drug of choice for patients aged 1-12 years with compensated liver disease. Success rates for suppression of viral replication range from 20%-50% in western countries, compared to 8%-17% in untreated controls.[53] In the largest multinational, randomized, controlled trial of IFN-alfa therapy in children to date, 26% of treated children became negative for markers of viral replication (HBeAg and HBV DNA) at the end of treatment, compared to 11% of untreated controls, and this rose to 35% in children whose baseline ALT was at least twice ULN. HBsAg seroconversion occurred in 10% of children in the treatment group, compared to 1% in the untreated group.[28] Factors associated with therapeutic response in children with chronic HBV infection were ALT $\geq$ 2 times ULN, female sex, low level of HBV DNA, younger age, and active inflammation on liver biopsy. Other data suggest that children under 5 years of age may have an enhanced response to IFN-alfa.[54-56] Peg-IFN has not been tested or approved for use in children in the United States. However, a recent update of the Swedish national recommendations for treatment of chronic HBV infection recommends the use of peg-IFN in children.[57]

The standard course of treatment with thrice weekly IFN-alfa is 6 months. Development of resistance has not been observed. HBeAg seroconversion may occur during or anytime up to 1 year after the end of IFN-alfa therapy. In one study, 18 of 70 children (26%) who were treated with IFN-alfa for 24 weeks became

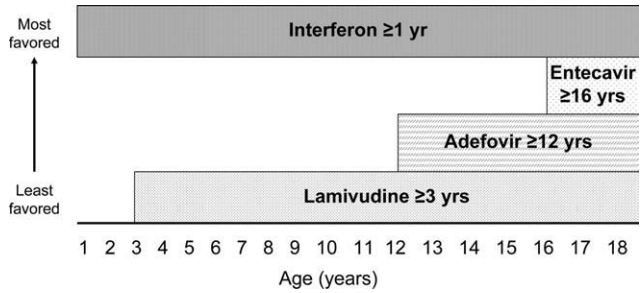

Fig. 2. Preferred use of nucleos(t)ide analogues that have been approved for use in children, based on age of the child.

negative for HBV DNA during the course of therapy, with an additional five children responding during the 24 weeks after cessation of therapy.[34] Therefore, it is not appropriate to declare treatment failure or to initiate another therapy until at least 6-12 months after treatment unless the child exhibits signs of decompensation. Children may experience moderate to severe side effects of IFN treatment, including flu-like symptoms, gastrointestinal disorders, neutropenia, and weight loss, all of which resolve after treatment is stopped. Mood disorders and personality changes have also been reported.[34] IFN-alfa is contraindicated in patients with cirrhosis, especially in those with decompensated liver disease, because hepatic failure and death may be precipitated. Long-term benefits in terms of reduction of cirrhosis and HCC have not been clearly documented for IFN-treated children, because most will eventually achieve HBeAg seroconversion even without treatment. However, if treatment shortens the duration of immune active HBV infection in children without cirrhosis, it could realistically be expected to mitigate hepatic injury and its consequences.

Nucleos(t)ide Analogues

As shown in Fig. 2, the order of preference for use of nucleos(t)ide analogues that have been approved for use in children is ideally entecavir, adefovir, and finally lamivudine, based on drug potency and risk of antiviral resistance. However, entecavir is labeled for use only in children age 16 years and older, and adefovir for ages 12 and older. Neither lamivudine nor adefovir is recommended as first-line nucleos(t)ide analogue treatment in adults due to the high risk of resistance for lamivudine and low potency and moderate risk of resistance for adefovir.

All three nucleos(t)ide analogues have been relatively recently approved for use in children and/or adolescents and therefore the follow-up of the clinical trials done to date is short. Treatment of children with chronic HBV infection has changed the natural history of the disease, and extended longitudinal observations are required to determine the clinical impact of earlier seroconversion for these children as they become adults.

Lamivudine. Lamivudine is labeled for treatment of chronic HBV infection in children of age 3 and older. In the pivotal randomized, controlled study of 288 children, virologic response (undetectable HBV DNA and loss of HBeAg) was observed in 23% of children receiving lamivudine compared to 13% in the placebo group following 52 weeks of treatment. In children whose baseline ALT was at least twice ULN the virologic response was 35%.[35] Of the 288 children, 276 were subsequently entered into a 24-month open-label treatment extension study, stratified on the basis of response in the previous trial, to either prolonged treatment or observation. Virologic response after 2 or 3 years of therapy was 54% in children without lamivudine-resistant virus. HBsAg loss was observed in 3%. Resistance rate was 64% in those children who received 3 years of lamivudine (i.e., 1 year in the primary study followed by 2 years in the open-label extension study).[58] A total of 151 of the children were then followed for 2 more years (5 years total). Long-term durability of HBeAg seroconversion was observed in 75% who had received placebo, 82% after lamivudine for 52 weeks, and more than 90% after lamivudine for at least 2 years.[59] In these studies, factors associated with response in children with chronic HBV infection were elevated baseline ALT and high baseline histology activity index (HAI) score.

The optimal duration of treatment with lamivudine is not known. For the pivotal trial, children were treated for 52 weeks and lamivudine was well tolerated. Children with HBeAg-positive chronic HBV infection should continue to receive treatment for at least 6 months after seroconversion. There is a high risk of emergence of viral resistance mutants to this agent, and the risk increases substantially over the time.[58] For this reason, practitioners should consider discontinuing lamivudine if there is incomplete viral suppression after 24 weeks of therapy, especially if there is no evidence of advanced liver disease. For those rare children with cirrhosis, a second agent such as adefovir could be added to lamivudine, or treatment changed to off-label entecavir. These alternatives are not considered appropriate for children with lamivudine resistance and milder liver disease because of the risk of induction of multi-drug resistance. Children need to be followed carefully for post-treatment ALT flares; although transient ALT elevations are not uncommon in patients in whom lamivudine is

discontinued,[60] they are rarely serious in those with mild to moderate liver disease.[59] However, alternative therapy may be indicated in those who develop a severe, maintained postdiscontinuation flare.

Adefovir Dipivoxil. Adefovir is labeled for use in children age 12 years and older, and is the preferred oral treatment option for children ages 12-15 (i.e., until they are old enough to receive entecavir) who clearly require treatment. The pivotal, multicenter, randomized, controlled study of 173 HBeAg-positive children aged 2-17 years with abnormal ALT of at least 1.5 times ULN showed significant adefovir antiviral activity (achievement of undetectable HBV DNA and normal ALT) in 12- to 17-year-old subjects, but there was no statistical difference between adefovir and placebo in subjects aged 2-11 years.[36] HBeAg seroconversion was noted in young children receiving this drug, and whereas none receiving placebo achieved HBeAg seroconversion, the difference did not reach statistical significance. No mutations associated with adefovir resistance were identified over the course of the study and the drug was safe and well tolerated by all age groups. However, the antiviral effect of adefovir is less than that of other agents and, as indicated above, this drug is no longer favored by adult practitioners who have more potent options.

The risk of antiviral resistance after 48 weeks of treatment is lower for adefovir than for lamivudine, and lamivudine resistant mutants are susceptible to adefovir. However, HBV strains that harbor the rtA181T/V lamivudine resistance mutation appear to have a diminished response to adefovir.[61] The optimal duration of adefovir treatment is not known. For the largest trial children were treated for 48 weeks. A follow-up study was conducted in which children who had not seroconverted received continued treatment for up to 2 additional years. Data analysis from that study is pending. Children with HBeAg-positive chronic HBV infection should continue on treatment for at least 6 months after seroconversion. Once again, it may be prudent to discontinue treatment if there is incomplete viral suppression after 24 weeks to minimize risk of resistance, unless advanced liver disease is present. Monitoring after cessation of treatment for several months is recommended, because posttreatment flares have been reported in adults.[62,63] These are generally mild. Data regarding frequency of posttreatment flares with adefovir in children are not yet available.

Entecavir and Newer Medications. A phase 2b (pharmacokinetics and efficacy) clinical trial of entecavir in patients as young as 2 years old is currently underway, and a phase 3 study has begun. Tenofovir is currently being tested in an adolescent HBV cohort. However, there is no preparation suitable for use in young children who require a liquid medication with more dosage flexibility. A pediatric study is being considered for telbivudine. Because the risk of resistance is so high in children, and the adverse lifetime consequences of resistance may outweigh the benefits of treatment, it might be prudent to refer children with significant liver disease who need treatment to specialized centers conducting off label treatment using entecavir or tenofovir.

Treatment Options for Special Circumstances

There are special populations (Table 2) and individual circumstances for which there are unlikely ever to be randomized controlled trials, and shared clinical experience is generally the specialist's guide for treatment decisions. Given the limited number of agents currently labeled for use in children, there may also be scenarios where the available options for a child are exhausted or inappropriate (e.g., a young child with cirrhosis who is nonresponsive or resistant to lamivudine, and for whom IFN-alfa would be contraindicated). In such cases, therapy must be individualized based on the best information available to the specialist at the time, including case reports, interim clinical trial study results, expert opinion, or extrapolation from labeled indications for antiviral agents approved for adults but not yet approved for children.

HIV/HBV coinfection is common in some regions of the world such as Africa,[64] and children emigrating from these regions may be infected with both viruses. Coinfection may also be found in adolescents who are injection drug abusers. Coinfected persons have a higher risk of progression of liver fibrosis,[65] and of development of resistance to lamivudine if it is the only drug active against HBV that is used in a Highly Active Anti-retroviral Therapy (HAART) regimen.[66] In addition, in coinfected persons in whom HAART has been successful, there is a risk of hepatitis B flare associated with immune reconstitution (rise in CD4 lymphocyte count).[67] Tenofovir plus lamivudine or emtricitabine is the recommended regimen in adults with HIV/HBV coinfection who require treatment either for HIV or for both viruses, and these may be viable options for HIV/HBV-coinfected children needing treatment.[68]

There are insufficient data from which to extrapolate recommendations for treatment of children with both HBV and HCV infections, although IFN-alfa (at higher HBV-recommended doses) with ribavirin could be considered in this unusual setting. Children with

both chronic HBV and chronic HDV infections have more severe liver disease than those with HBV alone. Studies in adults suggest that lamivudine is unlikely to be of much benefit, and IFN-alfa therapy may be the most prudent option.[69,70]

There are also special issues for pregnant teens. Although no studies have been done in pregnant adolescents *per se*, the considerations may be similar to those in pregnant young women, which have been discussed elsewhere.[71] In general, pregnant teenagers who are chronically infected with HBV should not be treated, but every effort should be made to make sure that their newborns are immunized immediately after birth with HBIG and the first dose of hepatitis B vaccine, preferably given in the delivery room as per CDC guidelines. Although there are a couple of small studies suggesting that lamivudine when given in the third trimester to mothers who are HBeAg-positive with high levels of HBV DNA in their blood, might decrease the risk of HBV transmission from mother to infant, these studies are controversial and need to be confirmed in a larger randomized trial. Because the risk of resistance with lamivudine is high, even if given for just a few months, the consensus of the panel is that nucleoside/nucleotide analogues not be given in the third trimester unless done under the auspices of a controlled clinical trial.

Monitoring During Therapy

Adverse Events

As with any therapeutic intervention, children require monitoring for adverse events while receiving treatment for chronic HBV infection. Among the four therapies available to children, adverse events are most common in association with IFN treatment, and include fever, flu-like symptoms, fatigue, depression, thyroid dysfunction and bone marrow toxicity. Most adverse effects of IFN can be managed symptomatically, but close monitoring for bone marrow toxicity and primarily neutropenia is required with regular CBC with differential. Drug discontinuation is rarely required. Because IFN-alfa is contraindicated in patients with decompensated cirrhosis, patients should be monitored closely for disease progression during IFN therapy. Nucleos(t)ide analogues are generally very safe, and serious sequelae such as lactic acidosis are rare when this class of drugs is used for treatment of HBV. Adefovir may cause renal injury, and, for all of these agents, dose adjustments may be required for patients with any significant degree of renal function impairment. Tenofovir has been associated with decreased bone mineral density in pediatric patients treated for HIV infection[72]; data regarding this side effect are not yet available from the adolescent HBV trial. Posttreatment flares may occur after any of the agents is discontinued, and it is prudent to check ALT at least monthly for several months after treatment is stopped, especially if HBeAg seroconversion has not yet been achieved.

Treatment Failure/Nucleos(t)ide Resistance

Primary nonresponse or partial response to HBV antiviral treatment can be related to pharmacologic factors, such as the level of antiviral potency of the drug and the drug's intrinsic barrier to resistance, viral factors, such as viral level and presence of resistance mutations, or to host factors such as variations in individual drug metabolism or patient compliance. Primary nonresponse is characterized by a <1 $\log_{10}$ decrease in viral load after 3 months of treatment. In nonresponders, HBV genotypic testing for resistance may be useful to help differentiate between patient noncompliance and viral genotypic resistance.

In patients who have achieved virologic response, secondary treatment failure or virologic breakthrough, may occur. This is characterized by a >1 $\log_{10}$ rebound in serum HBV DNA levels while still receiving treatment. This phenomenon is generally due to genotypic resistance, viral mutations that are known to confer resistance to nucleos(t)ide analogues. Virologic breakthrough may be followed by a rise in ALT levels, know as biochemical breakthrough.[4,73] There is a high risk of development of virologic breakthrough associated with lamivudine treatment, because a single mutation in the HBV genome can lead to resistance.[4] Resistance to lamivudine occurs at a rate of 10%-20% per year and approaches 70% in adults by 5 years. Children receiving nucleos(t)ide analogues should be monitored for virologic breakthrough by assessment of HBV DNA levels every 3 months. If a 1 $\log_{10}$ rise in HBV DNA level occurs in previous responders, genotypic testing for resistance, by either commercial line probe assay or HBV sequencing, is advisable.

There are both individual and public health consequences of resistance. In an individual patient, resistance can lead to a lower likelihood of HBeAg seroconversion, reversion of virologic and histologic improvement, increased rate of disease progression, severe exacerbation if the patient has cirrhosis, and risk of graft loss and death in liver transplant patients. A child harboring a resistant HBV strain will also have a limited number of effective treatment options as an

adult. In addition, transmission of drug-resistant strains to uninfected persons could occur and could have long-term public health ramifications.

Management of Resistance

Initiating treatment in children only when it is indicated is the best way to reduce the incidence and impact of nucleos(t)ide resistance. Drugs with optimal antiviral potency and a low incidence of resistance are most suitable for treating children, as for adults. Sequential nucleos(t)ide monotherapies and treatment interruptions should be avoided. Ideally, practitioners should strive to provide children and their caregivers with tolerable and convenient treatment regimens to foster patient compliance with consistent, full-length therapy, but effective treatments of this sort may not yet be available.

Management of drug-resistant chronic HBV infection in children is a particular challenge due to the limited number of therapeutic options labeled for use in children. The severity of liver disease based on histology can provide important information to guide decisions to stop or modify treatment.

Lamivudine monotherapy is not advisable because of the very high incidence of resistance with this strategy. Thus, a child already receiving lamivudine presents somewhat of a problem. If HBV DNA is undetectable by a sensitive PCR assay (i.e., complete viral suppression), lamivudine treatment could be continued, and the patient monitored for the development of resistance. If the patient has been receiving lamivudine for more than 24 weeks, and shows evidence of virologic breakthrough (i.e., HBV DNA is detectable or increasing) and the initial or repeat liver biopsy demonstrated at least stage 2 fibrosis, there are three options: (1) treatment may be stopped and the child monitored for flare, (2) another drug may be added such as adefovir, or (3) treatment can be changed to IFN. If hepatitis is severe, a second antiviral drug should be added. However, IFN is contraindicated in cases of decompensated cirrhosis.

Similarly, for a child who is already receiving adefovir and develops primary resistance or is nonresponsive, it appears best to stop treatment if only mild hepatitis is present. If moderate hepatitis is present, treatment may be stopped and the child monitored for flare. Alternatively, treatment may be switched to IFN, or lamivudine may be added (if the child has never received lamivudine). If hepatitis is severe, the panel prefers adding lamivudine if the child had never received this drug in the past. For children older than 16 years who are either nonresponsive or develop resistance, adult treatment guidelines may be followed.

Indications for Stopping Oral Nucleos(t)ide Analogue Therapy

Under normal circumstances, when there is no evidence of antiviral resistance, and no severe adverse events that require cessation of therapy, children being treated with nucleos(t)ide analogues continue on therapy for a minimum of 12 months. Often significantly longer treatment is required, even though this is not included in drug labeling. Children with HBeAg-positive chronic HBV infection who have complete viral suppression and HBeAg seroconversion should have at least 6 months of consolidation therapy, but the optimal duration has not been elucidated. Adults are treated for at least 6 months and up to 12 months after HBeAg seroconversion. Children with HBeAg-negative chronic hepatitis B may need indefinite treatment, as stopping treatment in adults in 1 to 2 years results in an 80%-90% rate of relapse.

Development of virologic resistance is not an absolute indication for stopping treatment with a particular nucleos(t)ide analogue. Histologic evidence of the severity of the hepatitis is an important criterion for deciding whether to stop therapy, change therapy, or add another antiviral drug for combination therapy

In cases of patient nonadherence, treatment should be stopped. Close observation is preferable to repeatedly starting and stopping these agents. This strategy preserves treatment options for the future by decreasing the likelihood of drug resistance. Whenever treatment is stopped for any reason, children should be monitored every 1 to 3 months for several months for hepatic flare, then every 6 months thereafter.

Knowledge Gaps/Areas for Future Study

The most recent treatment guideline for adults recommends peg-IFN, tenofovir, or entecavir as first line HBV therapies.[4] A challenge for pediatric practitioners is the fact that peg-IFN and tenofovir have not yet been evaluated in children, and entecavir is labeled for use only beginning at age 16 years, relegating the majority of children to treatment regimens that are considered second line for adults. Compounding the problem of a limited number of drugs for children is the lack of information available regarding combination therapy in children. Table 4 highlights areas where additional research could help advance the

Table 4. Knowledge Gaps/Areas for Further Study

What is the role of currently available therapy in the immune tolerant pediatric patient?
– randomized trials are needed
Will there be other agents effective in the treatment of the immune tolerant patient?
Should children be treated with combinations of agents?
What is the role of HBV genotyping with respect to therapy?
Is there a role for noninvasive biomarkers of liver fibrosis in children?
Are there additional predictors of response to therapy in children?
– early changes in viral DNA
– quantitative changes in HBsAg and HBeAg
How does a family history of liver disease impact treatment decisions?
How does HCC risk impact treatment decisions?
What is the impact of treatment on HCC risk?
How should children with HBV be monitored for HCC?
How should treatment be modified in pediatric nonresponders?
How should children coinfected with HIV, HCV, or HDV be treated?

understanding of HBV pathogenesis and treatment decisions in children.

Summary

Chronic hepatitis B infection in children presents a therapeutic challenge for the pediatric practitioner. Decisions regarding selection of patients for treatment, appropriate timing of treatment, and the choice of antiviral therapy are complex. Although the majority of children will not require treatment, routine monitoring for progression of disease is essential so that the child who might benefit from treatment is not missed. Therapeutic options for children are currently limited, and the potential for viral resistance to current and future therapies is a particular concern. Unnecessary early therapy with nucleos(t)ide analogues can result in development of resistance, thereby limiting treatment options later in life. In addition, the potential long-term toxicities of currently approved therapies are not known.

Based on the data available at this time, it is the consensus of the panel that it is not appropriate to treat children in the immune tolerant phase (evidence of viral replication but with normal ALT), as there is no established benefit of treatment, IFN is not effective and there is a high risk of development of nucleos(t)ide analogue resistance. There is no indication for treatment of children in the inactive carrier state (normal ALT and no evidence of viral replication). For children in the immune active or reactivation phases (persistent ALT levels >1.5 times ULN, or >60 IU/L, whichever is lower, for at least 6 months and evidence of viral replication with HBV DNA $\geq$ 2000 IU/mL), liver histology can help guide treatment decisions. The benefit of treatment has not been established for children with minimal to mild necroinflammation and/or fibrosis, but a family history of HCC may argue in favor of treating these children. Children with moderate to severe necroinflammation and/or fibrosis are candidates for treatment. Outside of clinical trials, IFN is the agent of choice in most cases; however, practitioners must be alert for potential adverse effects. IFN is not appropriate for children with decompensated liver disease. Currently available nucleos(t)ide analogues are secondary therapies, and children who receive these agents may develop resistant HBV infection. There are selected circumstances in which treatment is indicated, regardless of DNA or ALT levels. These include children with cirrhosis, coinfection with HDV, rapid deterioration of liver function, or those who will receive immunosuppressive or cytotoxic chemotherapy.

There is still much to be elucidated about the appropriate use of HBV therapy in children. The long-term effects of early seroconversion on the overall course of the disease are not known, and the risk of emergence of drug resistant mutant strains is high. Resistant HBV strains impact not only the current and future treatment of the individual, but represent a major public health risk as these resistant viruses become more prevalent in the population as a whole. Children with chronic HBV infection at imminent risk for progression to serious liver disease should be identified, monitored closely, and treated if appropriate, but until more clinical data and therapeutic options are available, a conservative approach is warranted.

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