Recommendations for Screening, Monitoring, and Referral of Pediatric Chronic Hepatitis B

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KEY WORDS

hepatitis B, chronic, pediatrics, screening, disease management, liver

ABBREVIATIONS

HBV—hepatitis B virus
HCC—hepatocellular carcinoma
HBsAg—hepatitis B surface antigen
anti-HBs—antibody to hepatitis B surface antigen
ALT—alanine aminotransferase
HBeAg—hepatitis B e-antigen
anti-HBe—antibody to hepatitis B e antigen
ULN—upper limit(s) of normal
CDC—Centers for Disease Control and Prevention
AFP—α-fetoprotein

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abstract

Most children with chronic hepatitis B virus infection (persistent hepatitis B surface antigen–positive for >6 months) are asymptomatic and do not generally require treatment. These children are, however, at increased risk for severe complications later in life, including advanced liver disease and liver cancer. On November 11, 2008, the Hepatitis B Foundation, a nonprofit research and disease advocacy organization, convened a panel of nationally recognized North American pediatric liver specialists to consider and recommend an approach for the screening, monitoring, initial management, and referral of children with chronic hepatitis B. The panel developed recommendations to provide guidance to practitioners on determining what additional tests to conduct, how often to monitor on the basis of test results, and when to refer to a pediatric liver specialist to build a partnership between the practitioner and liver specialist to enhance the success of management of children with this lifelong infection. *Pediatrics* 2009;124:e000

The majority of children with chronic hepatitis B virus (HBV) infection have no signs or symptoms of chronic disease. It is for that reason that identification requires a heightened awareness on the part of physicians. Once identified, the next steps for a child with hepatitis B are often not clear. There are relatively few pediatric liver specialists who focus on hepatitis B in North America, and management guidelines specific for pediatric hepatitis B are lacking. Although most children with chronic HBV are asymptomatic and do not generally require treatment, these children can have progressive disease and are at increased risk for severe complications later in life, with some children going on to develop advanced liver disease and even liver cancer before their third decade. HBV infection acquired via maternal-fetal transmission is associated with the highest risk of hepatocellular carcinoma (HCC).[1] Although HCC is uncommon in the pediatric time frame, these facts compel us to be vigilant. Lifelong monitoring for progression of disease is critical. It is important for practitioners to understand and use appropriate surveillance, monitoring, and timely referral. Our understanding of hepatitis B disease and the armamentarium of available therapies has grown substantially in recent years, calling for a fresh look at clinical practices and approaches. On November 11, 2008, the Hepatitis B Foundation, a nonprofit research and disease advocacy organization, convened a panel of nationally recognized North American pediatric liver specialists from around the country to begin to discuss approaches to diagnosis, initial management, and referral of children with chronic hepatitis B infection. This article was designed to provide guidance to primary care practitioners on which

children to screen for HBV and on the initial management of chronic HBV, specifically, additional tests that should be considered, plans for monitoring, and indications for referral of HBV-infected children to a pediatric liver specialist. The overall goal was to develop a strategy for primary practitioners and pediatric liver specialists to partner in the long-term care of children with chronic HBV. (In this article, children are defined as persons through 17 years of age.)

EPIDEMIOLOGY

Despite the introduction of universal infant vaccination in 1991 in the United States, hepatitis B infection has not been eradicated. Much of the world's population lives in areas where the lifetime risk of contracting hepatitis B exceeds 60%.[2] In the United States, the incidence of acute cases of hepatitis B have declined significantly, especially in children, but chronic hepatitis B remains a substantial problem for a number of reasons including vertical transmission, immigration to the United States from areas of endemicity, and infection from hepatitis B surface antigen (HBsAg)–positive household contacts. Infants and young children are at particular risk for developing chronic hepatitis B infection after exposure to the virus. Ninety percent of infants infected as a neonate and 25% to 50% of children between the ages of 1 and 5 years who are acutely infected with HBV will progress to develop chronic infection, whereas <5% of symptomatic and only 5% to 10% of asymptomatic infected adults and teenagers will develop chronic hepatitis B. In the United States, the total number of persons with chronic hepatitis B is thought to be almost 2 million,[3] with many infected adults having acquired their infection during infancy or childhood. Chronic infection is not only a public health concern but also a concern for the individual. Among adults who acquired chronic hepatitis B infection as an infant or child, ~15% to 25% overall die a premature liver-related death.[4–7] Chronic HBV is especially common in certain populations in the United States, including Asian Americans. Identification of infection and delivery of appropriate care and counseling have been hampered by low health literacy.[8,9]

VACCINATION AND PREVENTION

Hepatitis B vaccination is the most effective approach to preventing HBV infection. Over the past 2 decades, recommendations have evolved into a comprehensive strategy to eradicate HBV infection. The US Advisory Committee on Immunization Practices (ACIP) recommends that all infants be vaccinated against HBV beginning at birth, and all children <19 years of age who have not been vaccinated previously should also be vaccinated.[10] Because of the successful implementation of HBV vaccination in the United States, the incidence of acute hepatitis B infection in children <15 years of age declined by 98% between 1990 and 2006.[11–13] Currently, the majority of new cases of HBV in children in the United States are those who were not fully vaccinated, in many cases homeless children, international adoptees, children born outside the United States (even if the child supposedly received hepatitis B vaccine in their birth country), or those who were born to HBsAg-positive mothers and did not receive immunoprophylaxis or the birth dose of vaccine in a timely fashion. Unfortunately, breakthrough infection occurs in ~5% of infants born to HBV-infected mothers even after appropriate immunoprophylaxis and vaccination.[14] For issues of compliance, and to prevent perinatal transmission, the ACIP recommends administration of 1 dose of hepatitis B immunoglobulin and the first dose of vaccine to newborns of HBsAg-positive mothers within 12 hours of birth rather than begin the series at a subsequent appointment. Completion of the 3-dose hepatitis B vaccination series by 6 months of age is recommended for all infants, and postvaccination testing of infants born to HBsAg-positive mothers for protective antibody response (antibody to hepatitis B surface antigen [anti-HBs]) and HBsAg is recommended at between 9 and 18 months of age to determine if infection has been prevented. The United States has yet to achieve 100% compliance with the universal vaccination recommendation, however. It is estimated that 92% of the infants with potential HBV exposure are receiving the appropriate immunization and prophylaxis in a timely fashion. This number does not reflect regional variations. States such as Louisiana, for example, are in the range of 78% to 82% compliance.[15] It has also been shown that infants born to women of unknown HBsAg status are less likely to receive appropriate preventive immunization at the time of delivery.[16]

PATHOPHYSIOLOGY

Chronic HBV infection, defined as detectable HBsAg for at least 6 months, is marked by 4 phases of disease that are important in determining responsiveness to therapy and risk of disease progression. Most pediatric patients, especially younger children, are in the immune-tolerant phase, which is marked by DNA levels that well exceed 20 000 IU/mL (1 million copies per mL), a normal serum alanine aminotransferase (ALT) level, and minimal liver inflammation and fibrosis. HBsAg and hepatitis B e-antigen (HBeAg) are detectable in serum during this phase. In the immune-tolerant phase, currently available antiviral therapies are generally ineffective at maintaining suppression of HBV, and there is a risk of HBV resistance occurring over time; therefore, children in this phase of in-

fection are not treated. During the immune-active phase, serum viral DNA levels decline, there is elevation of the ALT level, and inflammation and fibrosis can develop in the liver. HBsAg and HBeAg remain detectable in serum. Most children are still without signs or symptoms of disease, yet the longer a person remains in the immune-active phase, the more likely he or she will develop chronic liver damage, cirrhosis, and HCC. Most children will eventually have undetectable HBeAg and develop antibody to the HBeAg (anti-HBe) during childhood or early adulthood, except for those children infected with HBV genotype C, the genotype commonly found in Asia. There is increasing evidence that what was previously attributed to ethnic differences is most likely influenced by genotype. A recent study by Livingston et al[17] of a cohort of 1158 people found that the mean age of HBeAg clearance was 47.8 years for genotype C, whereas for genotypes A, B, D, and F, the mean age of HBeAg clearance occurred before 20 years. Furthermore, genotype C is more likely to revert to an HBeAg-positive state and more likely to be transmitted vertically. When HBeAg becomes undetectable and anti-HBe is present, most persons move into the inactive HBsAg-carrier phase, in which the viral DNA level is low (usually <2000 IU/mL [10 000 copies per mL]) or undetectable, the ALT level normalizes, liver histology is without inflammation, hepatic fibrosis may regress, and the risk of cirrhosis and HCC declines. Another phase is the reactivation phase, which occurs in 20% to 30% of patients.[18] In this phase, viral DNA levels increase, whereas HBeAg remains undetectable. The ALT level may be either normal or elevated. This is also termed e-antigen–negative chronic hepatitis B and is usually caused by infection with a mutant virus. In addition, some persons may move directly into this phase without going into an inactive HBsAg-carrier phase. It is important to recognize this phase of infection, because the viral variant is more virulent and may require antiviral therapy to prevent liver damage from occurring over time.

Recent findings regarding the pathophysiology of HBV liver infection are particularly noteworthy for the practitioner. In a study of Asian subjects, 20% to 25% of individuals with chronic hepatitis B developed severe hepatic fibrosis before the age of 25 years.[19] These individuals most likely acquired their disease in childhood and may have experienced a prolonged period in the immune-active phase. The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study suggested that during the immune-active phase, high HBV DNA levels and elevated ALT levels are associated with greater risk of cirrhosis and HCC.[20–22] In this study of adults whose average age was mid-40s, serum ALT levels as low as twice the upper limit of normal (ULN) were associated with progression to cirrhosis and HCC. These findings have prompted a new, more aggressive approach to the treatment of adults during the immune-active phase of chronic hepatitis B. The new guidelines for chronically infected adults have led to a heightened awareness among pediatric liver specialists that treatment during a prolonged immune-active phase is important for decreasing an infected child's risk of developing cirrhosis and/or cancer later in life. In addition, a strict linkage of ALT level with progression of liver disease is not always apparent, especially in children.[23] Practitioners need to rigorously monitor HBV-infected patients at regular intervals (every 6 to 12 months) and refer to a pediatric liver specialist any patient who has elevated ALT and HBV DNA levels. Vaccination, screening, referral for treatment at early time points, and lifetime monitoring are essential for successful management of chronic HBV infection in children.

SCREENING AND REFERRAL

The panel collectively endorses the updated (2008) Centers for Disease Control and Prevention (CDC) guidelines for HBV testing and recommendations for evaluation and management for chronically infected people.[11] A notable change in the recent update is the recommendation to screen all individuals born in geographic regions with an HBsAg prevalence of ≥2%, revised from ≥8% in the earlier guidelines. This CDC update aimed to improve identification of immigrants who acquired HBV in their country of origin. Previously, international adoptees were commonly screened for HBV, but children who immigrated with their intact families were not. The CDC also recommends that children born in the United States to immigrant parents from endemic areas be screened, and all children born to HBsAg-positive mothers should be tested (generally at 1 year of age). In addition, children who live in a household with a known HBsAg-positive person(s) should be screened. Even those who received vaccine but were not ever tested for HBV infection should be tested in case they were infected before vaccination or did not develop an adequate response to the vaccination (Table 1).

Serum HBsAg, along with anti-HBs, is the most effective screening tool for HBV infection. HBsAg is detectable in virtually all individuals with chronic infection, even when HBV DNA levels are undetectable. A lack of anti-HBs identifies susceptible children who need vaccination. Children found to be HBsAg-positive should be retested 6 months later to document chronic infection. As noted above, serum ALT levels are not elevated in children in the

TABLE 1 Children Who Should Be Screened for Chronic HBV Infection[11]

Children born in a country endemic for HBV, even if they received hepatitis B vaccine in their country of origin, including
All of Asia
All of Africa
South- and mid-Pacific Islands
Europe (Eastern and Mediterranean countries), Greenland, and Russia
Middle East
South America: Amazon Basin
Caribbean
Indigenous populations from the Arctic, Australia, and New Zealand
Children born in the United States to immigrant parents from endemic areas
Infants born to HBsAg-positive mothers
Children living in a household with an HBsAg-positive individual, including those children who received hepatitis B vaccine after birth who were not screened before vaccination

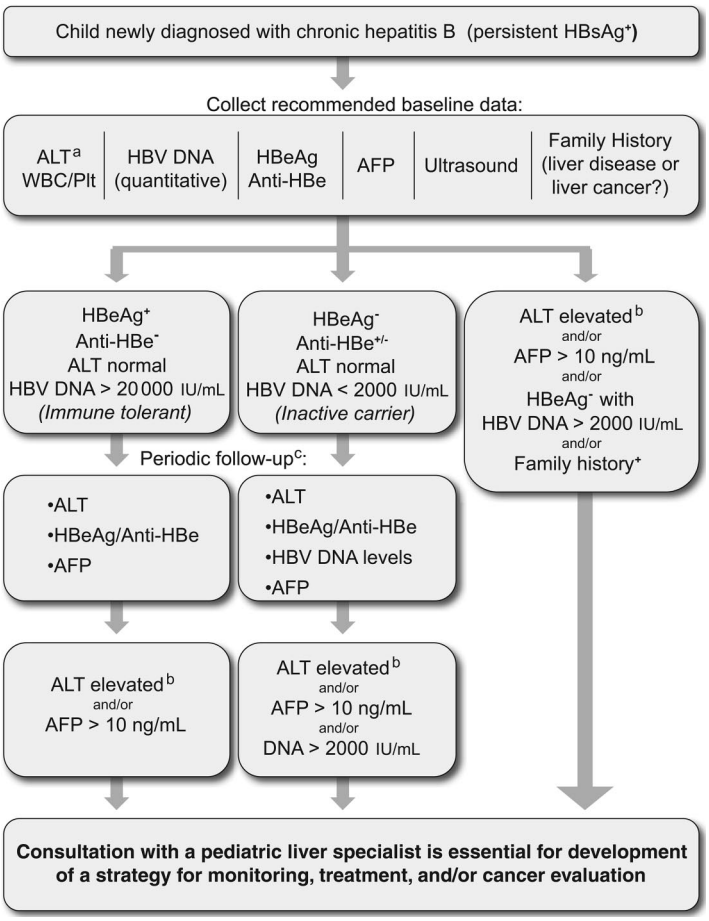

FIGURE 1
Recommended approach to monitoring children with chronic hepatitis B (persistent HBsAg-positive) infection. Any child who has an elevated ALT or AFP level, has a positive family history of HCC, or is HBeAg-negative but has an HBV DNA level of >2000 IU/mL should be referred to a pediatric liver specialist. [a] ALT level and white blood cell/platelet (WBC/Plt) count are generally included in the baseline evaluation as part of a hepatic function panel and complete blood count, respectively. [b] The ALT level should be considered elevated if greater than the testing laboratory ULN or >40 IU/L, whichever is lower. [c] Measure ALT and AFP levels every 6 to 12 months and HBeAg/Anti-HBe and HBV DNA levels every 12 months. Many pediatric specialists also consider ultrasound every 1 to 2 years appropriate (particularly with a family history of HCC or if the ALT or AFP level is elevated).

immune-tolerant phase; therefore, measurement of ALT is not an appropriate screening method for detecting HBV infection.

Once a child is identified as having chronic hepatitis B infection, the panel recommends collection of a set of baseline data and an initial consultation with a pediatric liver specialist. Figure 1 illustrates the recommended approach to monitoring children with chronic HBV infection. Specifically, the panel recommends that the following be included in the initial evaluation: ALT level (usually measured as part of a hepatic function panel); white blood cell and platelet counts, because low values are surrogate markers for advanced liver fibrosis (usually measured as part of a complete blood count); hepatitis B serology, specifically serology for HBeAg and anti-HBe, and quantitative HBV DNA, used in conjunction with the ALT level to determine the phase of disease; baseline liver ultrasound, used for crude assessment of liver texture and nodularity as well as spleen size; α-fetoprotein (AFP) levels, used to stratify risk of HCC; and family history of liver cancer or liver disease. Children who are HBeAg-positive, with normal ALT and AFP levels, should be reevaluated every 6 to 12 months, as described in Fig 1, along with continued monitoring of HBeAg/anti-HBe status. In this immune-tolerant phase, there is little risk of disease progression or HCC, and current therapies are ineffective. However, if the ALT level is elevated, the child is at risk for progression of liver disease and also may be a candidate for treatment. If HBeAg is undetectable yet the HBV DNA is detectable, then e-antigen–negative chronic hepatitis B has developed. In these latter 2 scenarios, the pediatric liver specialist may be particularly valuable for outlining a treatment plan and assessing extent of liver disease.

In the past 5 years the definition of ALT elevation has been scrutinized and revised with the new ULN being recommended for adults. For adult men, the ULN is 30 IU/L and for adult women, 19 IU/L.[24] However, the ULN for children have not been established. Therefore, it is recommended that adult guidelines be applied to the older teenager. For younger children, the ULN for ALT can vary according to laboratory and

age. In the absence of guidelines for children, the panel recommends that the ALT level be considered elevated if it is greater than the testing laboratory ULN or >40 IU/L, whichever is lower.

Children with a family history that is suspicious for hepatitis B–related cirrhosis or liver cancer should be considered to be at high risk, and a pediatric liver specialist should be consulted concerning the frequency of appropriate monitoring, taking into consideration the age of the patient and the specifics of the family history.

AFP is a marker of risk of HCC, but for children as well as adults, an elevated AFP level alone often does not indicate whether HCC is present. AFP elevations commonly occur with active liver inflammation and during pregnancy. Therefore, the AFP level is best used to stratify risk categories. In a population-based study of children and adults, AFP level was useful in identifying most children who developed HCC at a treatable stage, and a normal AFP level had a high negative predictive value for HCC.[25] In the absence of pediatric-specific studies on the usefulness of AFP levels, the panel endorses periodic AFP testing. Increasing serum AFP levels correspond to increasing HCC risk, and an AFP level of >10 ng/mL merits ultrasound evaluation for nodules and referral to a pediatric liver specialist for further evaluation and guidance. Although HCC associated with HBV is a rare event in childhood, it is important to remember that some children develop HCC without cirrhosis and can do so before reaching adulthood.[26,27] Furthermore, children with documented cirrhosis, a family history of HCC, and an elevated AFP level should be regularly screened for HCC at 6-month intervals with liver ultrasound and AFP-level measurement.

In general, the panel did not recommend routine monitoring of HBV DNA levels of children with detectable HBeAg and normal ALT levels. During the immune-tolerant phase, when the child is not a candidate for treatment, DNA levels may exceed 20 000 IU/mL and are thought to have little predictive value regarding the risk of cancer or cirrhosis. Likewise, children in the inactive HBsAg-carrier phase (anti-HBe–positive and normal ALT level) do not need monitoring of HBV DNA levels unless the ALT level becomes elevated, which may signify reactivation of HBV. However, children in the inactive HBsAg-carrier phase do need to have their ALT levels monitored every 6 to 12 months for the rest of their lives, and if the ALT level rises above normal, then the HBV DNA level should be assessed. It is important to remember that, as a result of the obesity epidemic in children, elevated ALT levels may be related to nonalcoholic fatty liver disease (NAFLD), an increasingly common finding in children with metabolic syndrome. Thus, some children with HBV infection in the inactive HBsAg-carrier phase may have elevated ALT levels resulting from NAFLD or other causes, but as expected in this phase, the HBV DNA level will not be elevated above 2000 IU/mL (10 000 copies per mL).

During the immune-active phase, the HBV DNA level can be helpful in designing a treatment plan (eg, HBV DNA levels may predict the likelihood of response to some treatment regimens, but it might only be measured if treatment is being considered). During the inactive HBsAg-carrier phase, DNA levels are undetectable, and it is during this phase that monitoring DNA levels can be useful to identify reactivation; thus, HBV DNA may be measured annually. The panel concluded that there was little value in routine monitoring of HBV DNA levels for those children with normal ALT levels, but routine monitoring is useful for those who are in the immune-active phase and being considered for treatment and for those in the inactive HBsAg-carrier phase to detect reactivation.

The panel did not reach a consensus regarding the frequency of ultrasound after a baseline examination. For the majority of infants and toddlers, cancer and cirrhosis are unlikely events. Even for young school-aged children the risk is minimal. Given the infrequency of these events before young adulthood, there is no evidence-based guidance for ultrasound monitoring. For adolescents, many pediatric liver specialists adopt the same guidelines used by adult hepatologists and perform ultrasound every 6 months for those with cirrhosis or an elevated AFP level and/or a family history of HCC.

In summary, adult treatment guidelines are rapidly evolving as an increasing range of therapies become available, as multidrug regimens are studied, and as interest in developing treatments for individuals with normal ALT levels grows. At this time, however, many of these newer therapies and strategies have not been adequately evaluated in children. The panel recommends that any child with an elevated ALT and/or AFP level and/or a positive family history for liver disease, especially liver cancer, be referred to a pediatric liver specialist who will advise on opportunities to treat and/or the need for further evaluation. The specialist will also recommend a strategy for long-term monitoring. In more urban areas, a local pediatric liver specialist often assumes responsibility for monitoring, whereas in more rural areas in which a specialist may not be geographically accessible, it may be primary care practitioners who continue to monitor and treat in consultation with the specialist.

TREATMENT AND LIFELONG MONITORING

Response of children to therapy is, so far, similar to that of adults, but the number of approved therapies for children has been limited. For adults, there are 7 antiviral drugs that are currently approved by the US Food and Drug Administration for use as initial therapy for chronic hepatitis B: 2 forms of interferon (interferon alfa-2b and peginterferon alfa-2a) and 5 nucleos(t)ide analogs (lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxil fumarate). For children, 4 of these therapies are currently available: adefovir is labeled for ages 12 and older; entecavir is labeled for ages 16 years and older; interferon alfa-2b is approved for use in children as young as 12 months of age; and lamivudine may be used starting at 3 years of age.

Despite 4 possible therapies, only 2 are approved for younger children. The decision to initiate treatment is still complicated and evolving. Lamivudine and adefovir are among the less potent options, but their use is not without risk. For lamivudine, the development of drug resistance is a significant concern. A study by Sokal et al[28] showed a resistance rate of 64% in children who received lamivudine for 36 months. If possible, lamivudine monotherapy should be avoided because of the high incidence of resistance observed with this treatment and the concern that it will affect future treatment options. Adefovir is a less potent antiviral drug against HBV, and increasing resistance to adefovir occurs over time.[29] Practice is rapidly evolving, and these once-recommended medications are now the least favored options among adult hepatologists. Development of resistance to interferon has not been observed, and although efficacy in adults is variable, young children (≤5 years old) may have an enhanced response to this drug, but adverse effects remain a concern.[30,31] In addition to the clinical impact drug resistance has on the patient's prognosis (decreased seroconversion, increased rate of disease progression) and the lifelong treatment challenges that face a child who harbors a resistant virus, there are public-health ramifications including the transmission of drug-resistant strains to others. As such, children who receive nucleos(t)ide antiviral therapy, alone or in combination, should be monitored for the development of resistance by periodic assessment of HBV DNA and ALT levels, as suggested by several published adult guidelines.[32,33]

Antiviral therapy is generally reserved for those who have active liver disease, as indicated by monitoring tests such as ALT levels (generally those who have moved from the immune-tolerant phase to the immune-clearance phase). For children who are HBeAg-positive with elevated ALT levels and compensated liver disease, an observation period of 6 to 12 months should be considered to determine if spontaneous HBeAg seroconversion occurs. There are many unanswered questions that play into the decision to initiate treatment with antiviral therapy, not least of which are the potential efficacy, duration of therapy, and risk of drug resistance in view of the limited therapeutic options for children.

Again, a successful partnership between the primary practitioner and pediatric liver specialist can enhance the success of screening, initial management, and monitoring of children with this lifelong infection.

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