Epidemiology and Natural History of Hepatitis B in Children

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Key Concepts

- Patients in countries with high HBV endemicity tend to have perinatal transmission of hepatitis B, whereas those in countries with low endemicity have horizontal infection in adolescence or early adulthood.
- Universal infant immunization could effectively reduce the prevalence of HBV infection to approximately 10% of the prevalence before the vaccination program.
- Important factors affecting HBsAg seroconversion included maternal HBeAg status, virus genotypes, and host effects.

Keywords Epidemiology • Acute hepatitis B • Chronic hepatitis B • Fulminant hepatitis B • Hepatocellular carcinoma • Hepatitis B e seroconversion

Introduction

Hepatitis B virus (HBV) infection is a worldwide health problem and may lead to acute, fulminant, or chronic hepatitis; liver cirrhosis; and hepatocellular carcinoma (HCC) [1]. Approximately two billion people in the world have been infected by HBV, and 350 million of them are chronically infected, with a 25% of mortality risk related to the sequelae of hepatitis B. Roughly, an estimated one million deaths annually are attributed to HBV infection [2, 3]. Therefore, the burden of HBV infection is huge, and understandings of the natural history of HBV infection are extremely important to design preventive and therapeutic strategies.
Epidemiology of Hepatitis B Virus Infection in Children Before the Era of Immunization Programs

Global

The prevalence of HBV infection varies in different countries or regions in the world (Fig. 1) as well as in different ethnic groups. HBV endemicity has been classified into three categories, high (>8%), intermediate (2–8%), and low (<2%), depending on the prevalence of hepatitis B surface antigen (HBsAg) seropositivity. The highly endemic areas in the world include East and Southeast Asia, the Pacific, sub-Saharan Africa, and parts of southern Europe. In North America, and western and northern Europe, HBV infection is relatively rare, with a prevalence rate of around 0.1%.

North America

Overall, the prevalence of HBV infection in this region is low. In the United States, the Third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994, revealed that the HBsAg seropositive rate was 0.41%, and the prevalence of previous or current HBV infection, i.e., seropositive antibodies against hepatitis B core antigen (anti-HBc), declined from 5.5 to 4.9%,
compared to the results from NHANES II in 1976–1980 [15]. The prevalence of HBV infection in both NHANES studies was low in children upto 12 years of age and increased thereafter in all ethnic groups. After the 1991 recommendation for universal hepatitis B vaccination in the United States, the incidence of acute hepatitis B among children has declined in all ethnic groups to 0.3 cases per 100,000 in 2002 [16]. In Alaska, 10 years after institution of the routine immunization program, the prevalence of resolved HBV infection by 9 years of age declined from 7.6 to 1.5%; the HBsAg-seropositive prevalence also declined from 3.1 to 0% [4].

In Canada, the prevalence of HBsAg seropositivity through the National Notifiable Disease Reporting (NNDR) system is estimated to be 0.5–1.0% of the population [17]. Most acute HBV infections are associated with injection drug use and heterosexual activities. Mother-to-infant transmission is not a major route of HBV acquisition in Canada. Nevertheless, infant routine vaccination strategies have successfully decreased hepatitis B carriage in North America [18].

**Europe**

The HBsAg seroprevalence in this region varies widely, ranging from 0.3 to 12%, even within a single country [19]. The most frequently reported risk factors for hepatitis B in Europe include heterosexual activity, injection drug use, male homosexual activity, perinatal exposure, and household contact with infected individuals [20]. By the end of 2002, 41 of the 51 countries of the World Health Organization European Region had implemented universal hepatitis B vaccination programs for infants or adolescents [21]. The universal vaccination program was introduced in Italy in 1991; population surveys in 1994–1995 showed a significant decline in hepatitis B prevalence and a 50% reduction in acute hepatitis B incidence [22]. Some very low prevalence countries, such as Denmark, Finland, Iceland, Ireland, Federal republic of Yugoslavia, Netherlands, Norway, Sweden, and United Kingdom, do not yet incorporate universal HBV vaccination for economic reasons.

**Asia-Pacific Region**

This area has countries with the highest prevalence level of endemic HBV infection (>8% HBsAg positivity) in the world, such as China, South Korea, Taiwan, Thailand and Vietnam [23]. Some countries in this area, such as Japan, Australia, and New Zealand, have low HBsAg prevalence rates. In the high endemic areas, perinatal infection and household contact with chronically infected patients during early childhood are the predominant modes of transmission [23]. For example, in Taiwan, before the implementation of a universal HBV immunization program, the HBsAg seropositivity rate of children in highly endemic areas was 5% in infants
and increased to 10% at 2 years of age, remaining at the same rate thereafter. However, the anti-HBc antibody seropositivity rate reached 50% by the age of 15 years. This suggests that most HBsAg carriers in this population were infected before 2 years of age due to perinatal or early childhood transmission [5, 24]. In low prevalence areas, HBV infection is acquired mainly in adolescents and adults. Childhood HBV infection in this population is concentrated in immigrants from hyperendemic areas and in high-risk groups, such as children of intravenous drug users.

**Africa**

After Asia, Africa has the second largest number of individuals with chronic HBV infection, approaching 58 million [25]. Although overall Africa is considered a high endemic area with 7–26% prevalence of HBsAg, Tunisia, Morocco, and Zambia have intermediate endemicity [26]. In some countries in western Africa, e.g., Senegal and Gambia, over 90% of the population are exposed to and become infected with HBV during their lives [27]. Because of high HBV endemicity, Gambia was the first country in Africa to implement a mass infant immunization program in 1990, and demonstrated a reduced HBV burden in children, with HBsAg prevalence decreasing from 10.0 to 0.6% [6, 7]. In contrast to Asia, where mother-to-infant transmission is an important route, horizontal transmission in early life is considered to be the predominant mode of transmission in most of sub-Saharan Africa [28]. In rural areas of west Africa, HBV infection rates increase rapidly from the age of 6 months, and by the age of 2 years, 40% of children are infected and 15% develop chronic infection. By the age of 10 years, 90% of children become infected and 20% are chronic carriers [29].

**HBV Transmission in Children**

Major routes of HBV transmission include perinatal infection, horizontal infection, sexual behaviors, and intravenous drugs use. The transmission patterns differ in countries according to HBV endemicity. In hyperendemic areas, perinatal and horizontal infections in childhood are responsible for most transmission of infection; in intermediate endemic areas, a mix of various routes of transmission are observed; and in low endemic countries, most new infections occur in young adults through sexual intercourse or injecting drugs. Perinatal transmission from HBsAg-positive mothers to their infants is an important route of transmission in children (Table 1), and accounts for 40–50% before and 90% after the HBV vaccination era of HBsAg carriers in endemic areas in Asia such as Taiwan [5]. The young age of HBV infection and maternal hepatitis B e antigen (HBeAg) seropositivity are important factors in determining chronicity in children [30–33]. Chronic HBV infection develops in 90% of infected neonates or infants but only in 1–5% of
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Approximately 90% of the infants of HBeAg-positive mothers become HBsAg carriers without HBV immunization, regardless of whether the HBsAg carrier rate in the population is high or low [35]. Although HBV is found in breast milk, breast feeding is permitted for the mother who is infected with hepatitis B, since this has not been implicated in transmission. It is widely accepted that most perinatal transmissions occur at or near the time of birth, since neonatal vaccination prevents newborn infection in about 80–95% of cases. Theoretical risks for HBV transmission at delivery include exposure to cervical secretions and maternal blood. Transplacental (intrauterine) transmission is presumed to cause the minority of infections not prevented by prompt immunization. An observational study from Taiwan described a lower (9.7%) transmission rate to infants of highly infectious mothers delivered after cesarean section in comparison to a higher (24.9%) rate of transmission after vaginal delivery [36]. Another study compared outcomes among three groups: 144 infants born by spontaneous vaginal delivery, 40 by forceps or vacuum extraction, and 117 by cesarean section [37]. All infants received HBIG and HBV vaccine at the recommended schedule. Chronic HBV infection was detected in the infants in 7.3, 7.7, and 6.8%, respectively, and response rates to immunization were similar in all groups. The authors concluded that mode of delivery does not influence the likelihood of HBV transmission. The effects of different modes of delivery have not been confirmed, and routine cesarean section is not recommended.

**The Effect of HBV Immunization in Children and Adolescents**

Universal hepatitis B vaccination programs in some hyperendemic countries have effectively reduced the prevalence rate and reduce the chronic HBV infection rate (Fig. 1). Countries or regions that were examples of early implementation of universal HBV immunization include Taiwan (1984), Hong Kong (1988), Israel (1989), Malaysia (1990), Gambia (1990), Italy (1991), Spain (1991), and the United States (1991).

Strategies of HBV immunization vary in different countries depending on the seroepidemiologic status and the resources of the countries (Table 2). All infants receive three or four doses of HBV vaccine in the universal HBV vaccination
program. Besides, hepatitis B immunoglobulin (HBIG) is given within 24 h after birth to infants of HBsAg- and HBeAg-positive mothers in some countries such as Taiwan [5], or to infants of HBsAg-positive mothers in the United States [4], Italy [8], Spain [9], etc. In countries with limited resources, maternal screening is not performed and no HBIG is given [38].

Taiwan has the longest experience with HBV immunization in the world, and has been a good example of a highly endemic area with a striking reduction in the burden of hepatitis B infection resulting from universal infant vaccination. HBsAg seroprevalence among Taiwanese children declined from 9.8% in 1984 to 0.5% in 2004 [5]; this universal vaccination program is poised to change Taiwan from a hyperendemic country to a low endemic country in the coming years. The HBsAg seropositivity rates declined to below 1% in most countries worldwide after universal infant hepatitis B immunization, regardless of the endemicity before vaccination [4–14] (Fig. 1).

Moreover, universal infant HBV immunization may reduce the incidence of HCC in childhood and early adulthood. The average annual incidence of HCC in Taiwanese children aged 6–14 years decreased from 0.52 to 0.54 cases per 100,000 children of the birth cohort born before the HBV vaccination program, to 0.13–0.20 cases in those born after the HBV vaccination program (P<0.01) [39–41]. According to a 20-year follow-up study of national cancer surveillance in Taiwan, prevention of HCC by universal HBV vaccination was observed not only in children but also extended to adolescents, with an age- and sex-adjusted relative risk of 0.31 for persons vaccinated at birth [42]. HBV vaccine is the first human vaccine demonstrated to prevent the development of cancer. In addition to the beneficial effects on prevalence of HBV infection and incidence of HCC, after the universal vaccination program was instituted, the mortality rate of fulminant hepatitis among Taiwanese infants declined by 68% [43, 44].

### Natural History of Hepatitis B Virus Infection in Children

Primary HBV infection can lead to acute hepatitis, fulminant hepatitis, or chronic infection under different conditions (Fig. 2). The interaction between virus and host determines the outcome of HBV infection.

<table>
<thead>
<tr>
<th>Maternal screening</th>
<th>Maternal status</th>
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<th>HBIG</th>
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*HBIG* hepatitis B immunoglobulin; *HBsAg* hepatitis B surface antigen; *HBeAg* hepatitis B e antigen
Acute HBV Infection

Acute HBV infection in children can be either symptomatic or asymptomatic; the latter is more common, especially in infants and young children. Acute infection runs a self-limited course and recovery is marked by hepatitis B surface antibody (anti-HBs) seroconversion. In symptomatic patients, the prodromal symptoms, including general malaise, anorexia, nausea, vomiting, and fever, may persist for several days to weeks. Some cases may have jaundice with or without light yellow stool. Hepatomegaly with tenderness on right upper quadrant of abdomen is typical; however, splenomegaly is uncommon. Alanine aminotransferase (ALT) levels do not increase until after viral infection is well established because time is required for virus-specific cytotoxic T lymphocytes to develop against HBV-infected hepatocytes.

In acute hepatitis B, HBsAg is the first marker detectable in the blood after an incubation period of 4–10 weeks, followed shortly by anti-HBc antibodies, which are predominantly of the IgM type in the early phase. Viremia is established by the
time HBsAg is detected, and the level of HBV DNA in acute infection is very high, frequently in the range of $10^9$–$10^{12}$ copies/mL ($10^8$–$10^{11}$ IU/mL). Circulating HBeAg can be detected early but is cleared rapidly in patients with acute hepatitis B, and anti-HBs antibodies appear within 6 months of disease onset in most patients.

Patients with acute hepatitis B usually recover completely from the liver damage with the development of lasting immunity to reinfection. However, with the development of sensitive assays for HBV DNA, it has been determined that low levels of HBV DNA may persist in the blood for up to 10 years in some patients, despite the presence of anti-HBs and specific cytotoxic T lymphocytes [45]. These observations suggest that HBV may not be completely eradicated after recovery from acute hepatitis, which supports reports of reactivation of HBV replication in patients with anti-HBs who receive chemotherapy or immunosuppression after organ transplantation [46].

**Fulminant Hepatitis B**

Fulminant hepatitis B should be considered in children who develop signs of liver failure, including coagulopathy, increasing bilirubin levels with declining aminotransferase levels, and a decreasing liver size, with or without hepatic encephalopathy, within 8 weeks after the initial symptoms of HBV [47]. Bernuau and colleagues defined fulminant hepatitis as hepatic encephalopathy developing 2 weeks after the onset of jaundice and subfulminant hepatitis as hepatic encephalopathy developing between 2 and 12 weeks after the onset of jaundice [48]. The incidence of fulminant hepatitis B is higher in infancy than in other age periods [43]. As the diagnosis of hepatic encephalopathy is difficult to establish in infants aged less than 1 year, the presence of hepatic encephalopathy is not an absolute requisite for fulminant hepatic failure in this age group [47, 49]. Fulminant hepatitis B can occur as early as 2 months of age in infants of HBsAg-positive mothers [43]. Maternal transmission is the most important route in infants with fulminant hepatitis B, especially in those of HBeAg seronegative mothers [50]. The mortality rate for infants with fulminant hepatitis B is high; 67% of affected infants die without liver transplantation [51]. Regarding older children or adolescents with fulminant hepatitis B, HBV infection occurs via a horizontal route (i.e., blood transfusion), which could potentially be prevented by infant vaccination or blood products screening [43].

**Chronic HBV Infection**

The natural course of chronic HBV infection, which is defined as persistence of HBsAg for more than 6 months, consists of three to four phases, according to the serum HBeAg and HBV DNA status.
Phase 1: Immune Tolerance Phase

Patients with chronic HBV infection have an initial immune tolerance state, which is characterized by the presence of HBeAg and high levels of HBV DNA due to rapid viral replication. The host is highly infectious, and an important source of horizontal infection in the family. During this phase, the host is usually asymptomatic and aminotransferase levels are usually normal, or mildly elevated. This phase is mostly seen in patients infected at birth or during early childhood. Infected children do not mount effective immune responses and exhibit immune tolerance, which leads to a high risk of chronicity in adulthood. Despite high levels of HBV DNA, liver damage in this phase is absent or minimal as a consequence of T cell immune tolerance to HBeAg and HBcAg [51]. Mechanisms underlying this immune tolerance are not well understood. During this phase, positivity of HBeAg and high HBV DNA levels in blood can persist for years after primary infection.

Phase 2: Inflammatory (Immune Active) Phase

When the host immune system becomes mature and begins to recognize HBV-related epitopes on hepatocytes, immune-mediated viral clearance and hepatocyte damage begin [52]. This phase, which lasts from several months to many years, is characterized by HBeAg positivity, high levels of HBV DNA, but now elevated serum aminotransferase levels, and active inflammation of the liver. In patients with perinatal or early childhood infection, transition from immune tolerance to immune clearance occurs mainly during the second or third decade of life [53]. Children in the HBe seroconversion stage mostly remain asymptomatic, or have mild non-specific symptoms such as general malaise, poor appetite, etc., making it difficult to detect the beginning of immune clearance. Serum ALT levels become elevated and fluctuate depending on the severity of liver damage during the virus–host interaction process. The peak levels of ALT often vary and are mostly <600 IU/mL. Active inflammation and hepatocyte damage are common histologic findings, but liver cirrhosis occurs uncommonly during childhood. Only 3.4% of 292 Italian HBsAg carrier children with elevated ALT were found to have liver cirrhosis at presentation [54].

The HBe seroconversion process, implying that the host loses the immune tolerance, varies in different individuals and is affected by age and maternal HBsAg status [55]. Some patients present with a flare of hepatitis followed by the disappearance of HBeAg and the presence of antibodies against HBeAg (anti-HBe); some have transient decreased HBV DNA levels without the clearance of HBeAg. In general, it takes around 2–7 years for the process of HBe seroconversion. The annual HBe seroconversion rate is less than 2% before the age of 3 years in a Taiwanese cohort; after 3 years of age, the annual HBe seroconversion rate gradually increased to about 5% [56].
Phase 3: Low Replication Phase (Inactive Carrier State)

After HBeAg seroconversion, most patients remain positive for anti-HBe antibodies and have gradual normalization of serum ALT levels. Patients in this phase are commonly referred to as “inactive HBsAg carriers.” HBV DNA can only be detected in 1% of anti-HBe-positive children using the less sensitive hybridization method but can be persistently detected in sera, usually at less than $10^4$ copies/mL, in the long term by assays that use the polymerase chain reaction (PCR). In an Italian study, 87% of 37 children after HBeAg seroconversion had detectable HBV DNA by PCR at 5-year follow-up and 58% had HBV DNA at 10-year follow-up [57]. Histologically minimal or mild hepatitis may be observed in children after HBeAg seroconversion.

Reactivation of HBV replication and a rise in ALT levels are not common in this phase in children; however, permanent liver damage and integration of the HBV genome may develop insidiously and gradually despite clearance of HBeAg. The subsequent development of liver cirrhosis or HCC is rarely observed but may happen during childhood [58]. In general, however, around 80% of childhood HCC occurs in children with anti-HBe antibodies [39, 59]. In an Italian long-term follow-up study for 29 years, the overall prognosis in horizontally infected children after HBeAg seroconversion showed that 2% of them progressed to HCC and 6% had HBeAg-negative hepatitis [60].

Phase 4: Reactivation Phase (HBeAg Negative Chronic Hepatitis B)

HBeAg seroconversion is generally considered as a good event indicating the cessation of liver inflammation and the beginning of an immune inactive status with low viral replication and minimal liver inflammation. However, HBeAg negative hepatitis is an important cause of liver injury after HBeAg seroconversion in adults. Subsequent reactivation of chronic hepatitis B occurs in up to one-third of inactive adult HBV carriers without reversion of HBeAg [61, 62]. This phase is characterized by the absence of HBeAg, the presence of anti-HBe antibodies, detectable HBV DNA levels ($<10^4$ copies/mL), serum ALT elevations, and histologically continuous necroinflammation of the liver. Most patients progress to this phase after a variable duration in the inactive carrier state, but some directly progress into this phase from immune clearance phase [63]. Selected HBV variants that cannot express HBeAg because of mutations in the precore or core regions of the HBV genome are thought to be the cause of HBeAg-negative chronic hepatitis [64].

The significance of HBeAg seroconversion occurring in childhood and young adulthood is clarified after a long-term follow-up study of 7–23.7 years [65]. In contrast to HBeAg seroconversion in adults, most children who underwent HBeAg seroconversion early had decreased viral loads, normal ALT levels, and uneventful courses after the HBeAg seroconversion. A prospective follow-up study of children with chronic hepatitis B showed that only 4.3% of 140 HBeAg seroconverters had re-elevated ALT after seroconversion [66].
Factors Affecting the Natural Course of Hepatitis B Virus Infection

Interactions between virus and the host may determine the natural course of HBV infection in an individual. Maternal factors may also affect the disease process in children who acquire HBV infection perinatally.

Maternal Factors

Children with HBeAg-positive mothers have higher rates of chronic infection (around 90%) after perinatal HBV transmission and lower rates of HBe seroconversion during long-term follow-up than those with HBeAg-negative mothers. This might be due to exposure to transplacental maternal HBeAg in utero since it has been demonstrated that there is absence of T cell response to HBCaAg in children of HBeAg-positive mothers [51]. In contrast, infants of HBeAg-negative mothers are prone to acute hepatitis B with recovery, or fulminant hepatitis B with a high mortality rate of approximately 67% [50].

Viral Factors

HBV genotype and variants also play a role. In one study, children with genotype C had late HBeAg seroconversion compared to that in those with genotype B during a 15-year follow-up period [67]. The HBV precore stop codon mutation [68], basal core promoter mutation [69], and core gene deletion mutation [70] may influence HBe seroconversion in children. An analysis of long-term followed 80 HBV-infected children revealed an increased proportion of the precore stop codon mutant of G to A mutation at nucleotide 1896 position after HBeAg seroconversion (50%), increased from 10% at the early HBeAg-positive stage [68]. An age-matched case–control longitudinal study showed that precore 1896 mutant accounts for half of childhood HBeAg seroconversion, and mutations of core promoter at nucleotide position 1752, 1755, and 1799 also have significant correlation with HBeAg seroconversion, whereas core promoter 1762/1764 mutations play a minimal role in HBeAg seroconversion in children [69].

Core gene mutations at codons 74, 87, and 159 are frequently seen in HBV-infected children with HCC, whereas codons 21, 147, and 65 are mostly seen in children with chronic HBV infection without HCC [71]. A long-term follow-up study demonstrated that core gene deletion mutants appeared in 4.9% of 365 children with chronic hepatitis B and mostly signified HBeAg seroconversion within 1 year [70]. Mutations of the human leukocyte antigen-A2-restricted T-cell epitope (TCE) on the HBsAg region were demonstrated to be positively
associated with early HBeAg seroconversion and higher ALT levels in children with chronic hepatitis B [72]. Children who have relatively lower HBV DNA levels (<1,000 pg/mL, equivalent to 5 × 10⁷ IU/mL) have a higher rate of undergoing HBeAg seroconversion during the subsequent 1–3 years than those with higher levels of viremia [56].

**Host Factors**

Children who have elevated ALT of >100 IU/mL often (66.7%, 16/24 cases) undergo HBeAg seroconversion during the subsequent 1–3 years, in comparison with 17.6% (27/153) in those with <100 IU/mL [56]. Cytokines also play roles in directly inhibiting viral replication and indirectly determining the patterns of host immune response [73]. Higher levels of serum interleukin (IL)-12 (>45 pg/mL) and IL-10 (>70 pg/mL) have been associated with early spontaneous HBeAg seroconversion in children. Variations in host cytokine genes may influence HBeAg seroconversion individually. The IL-10-1082 G/G and IL-12 beta −10993 C/G genotypes also predict early spontaneous HBeAg seroconversion [74]. In men, earlier-onset puberty, which refers to serum testosterone levels >2.5 ng/mL at 15 years of age, and increased enzyme activity of steroid 5α-reductase type II (SRD5A2) are associated with earlier spontaneous HBeAg seroconversion [75]. Nevertheless, additional determinant host factors still need to be examined.

**Conclusions**

Global control and elimination of hepatitis B virus infection remain an important and challenging task. The epidemiology, natural history, and treatment concerns are significantly different between children and adults with HBV infection. Decisions on when and how to treat are still difficult in asymptomatic children, and prevention should always be the preferred strategy. Any comprehensive strategy against HBV infection should include prevention of perinatal transmission, vaccination in considerable populations, and interruption of nosocomial transmission. The effects of global prevention of new infections will be apparent in decades.

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