REVIEW ARTICLE

Hepatitis B Infections in Neonates

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Abstract

Hepatitis B infections are estimated to affect more than 2 billion people worldwide. The overall prevalence of HBsAg positivity in plasma is reported to be 3.5%, but it varies depending on the geographic area. Mother-to-child infection is the predominant mode of transmission in high-prevalence areas. In exposed infants, universal hepatitis B vaccination and the administration of hepatitis B immunoglobulin (HBIg) within 12 hours following the birth can reduce the risk of perinatal infection. The rates of progression to chronic hepatitis B infection depend on the age of infection and are the highest in perinatally acquired infections, thus underscoring the importance of measures to reduce transmission. Timely identification and treatment of the affected pregnant women and immunoprophylaxis of newborn infants are of paramount importance to reduce the burden of chronic infection.

Keywords: Epidemiology, Hepatitis B, Maternal hepatitis B infection, Maternal-to-neonate transmission, Neonate, Prevention.

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Highlights

- Timely detection of maternal hepatitis B infection and antiviral treatment, in addition to the treatment of newborn infants with vaccination and administration of HBIg can reduce perinatal transmission by nearly 95%.
- The administration of tenofovir alafenamide fumarate (TAF) in pregnant mothers with high viral loads can reduce mother-to-child transmission of the hepatitis B virus (HBV).
- The recommended 3-dose vaccination series after the administration of a dose at birth should be completed by 24 weeks of postnatal age.
- Postvaccination anti-hepatitis B surface (anti-HBS) antibody titers that are more than or equal to 10 mIU/mL are seroprotective.
- Neonates with hepatitis B infections are mostly asymptomatic and need close follow-up and monitoring of liver enzymes and serology.
- Revaccination with the second series of hepatitis B vaccines for neonates who are hepatitis B surface antigens (HBsAg) negative but have anti-HBs antibodies less than 10 mIU/mL should be considered as per new Centers for Disease Control and Prevention (CDC) recommendations for the prevention of hepatitis B infection.

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Introduction

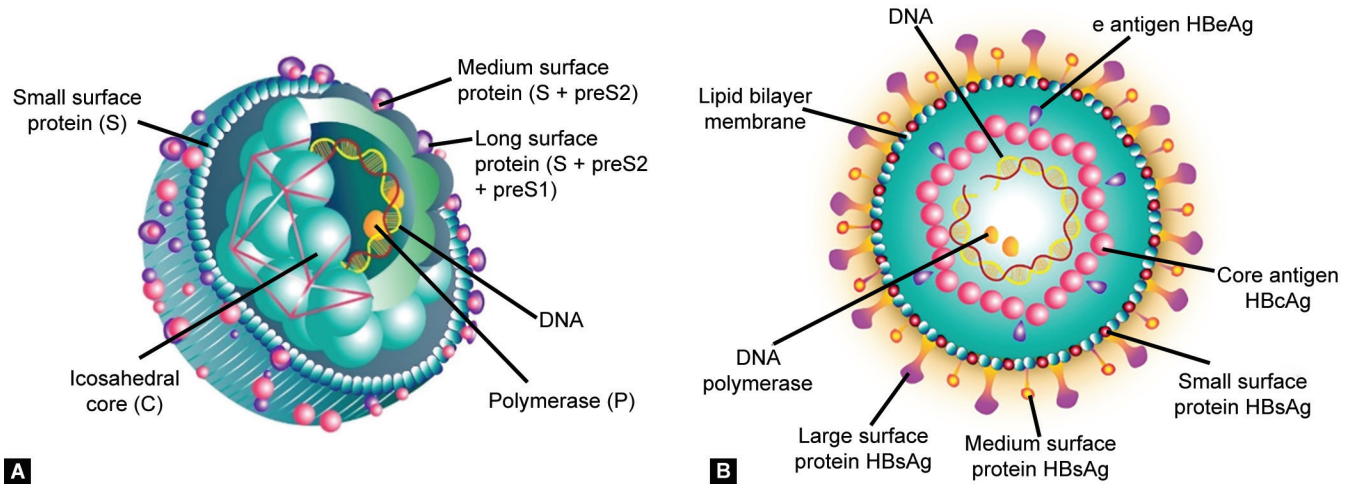
Hepatitis B is a global health problem and approximately 2 billion people worldwide have evidence of present or past Hepatitis B infection. Although HBsAg can be detected in up to 3.5% of infants worldwide, the incidence varies depending upon the geographical region.[1,2] The global prevalence of hepatitis B infections ranges between 4.2% and 6%.[3] In high endemicity regions such as in parts of China, the incidence can approach 7%.[4] Similarly, the incidence in India is estimated to be 3–4% with 40 million carriers.[5] This substantial variation is mainly related to differences in the age at infection, which is in turn inversely related to the risk of chronicity.[6]

The prevalence in children below 5 years of age reflects the effectiveness of hepatitis B vaccination coverage.[7] Latest estimates put the global prevalence figures to be less than 1%. The prevalence of chronic HBV infection in pregnant women is shown to be 0.8% but the risk of vertical mother-to-child transmission remains concerning.[8]

Structure

Hepatitis B virus is a small, double-stranded DNA virus[9] (Fig. 1). It resembles retroviruses in many aspects as it replicates through an RNA intermediate and can integrate into the host genome, which enables it to persist in infected cells.[10] Electron microscopy shows three types of viral-associated particles; the virion, spherical subviral particles (SVPs), and filamentous SVPs.[11]

The small subviral envelope spherules typically measure about 20-nm diameter. The filaments may be up to 22-nm long, contain the HBsAg and host-derived lipids without viral nucleic acids, and are non-infectious.[11] The fully-formed infectious HBV virions, known as the Dane particles, are enveloped, spherical, double-shelled structures that measure about 42-nm diameter.[12] The lipid envelope contains HBsAg, and encloses an inner nucleocapsid



Figs 1A and B: Structure of HBV. (A) Geometric structure of the spherical virion; (B) Major chemical components of the virion

comprised of the hepatitis B core antigen (HBcAg), polymerase, and the DNA genome. Hepatitis B e-antigen (HBeAg) is a HBV protein, produced by the HBcAg reading frame; it is an indicator of active viral replication. The viral polymerase is covalently attached to the 5′ end of the minus strand.[13] HBV has a partially double-stranded circular DNA genome of about 3.2 kilobase (kb) pairs with four overlapping open reading frames (ORFs: *S*, *C*, *P*, and *X*).[14]

The *S* ORF is subdivided into the pre-S1, pre-S2, and S regions and encodes three viral envelope proteins- large (L-), middle (M-), and small (S-) surface antigen (HBsAg).[15] The core or *C* gene has the pre-core and core regions and *C* ORF encodes the HBcAg or HBeAg depending on initiation of translation. The core protein forms the capsid structure while the pre-core ORF codes for a signal peptide which helps in secretion of HBeAg.[16]

The *P* ORF is the longest and encodes the polymerase (pol), a large protein comprised of the following three domains: The terminal protein domain, responsible for encapsidation and initiation of minus-strand synthesis; the reverse transcriptase (RT) domain, for genome synthesis; and the ribonuclease H domain, for facilitating replication by degradation of pre-genomic RNA (pgRNA).[17] After entry of the viral genome into the host nucleus, the single-stranded gap region in the viral genome is repaired by the viral pol protein thereby circularizing it into a covalently closed circular DNA (cccDNA) form, which serves as a template for transcription of genomic RNA.[18–21]

The *X* ORF encodes a 16.5-kd protein (HBxAg) which is involved in signal transduction, transcriptional activation, DNA repair, inhibition of protein degradation and may contribute to the oncogenic potential of HBV.[22,23]

Two direct repeats (DR1 and DR2) in the 5′ ends of the plus strand are required for strand-specific DNA synthesis during replication while the enhancer elements, En1 and En2, drive transcription of liver-specific expression of viral gene products.[9,24] The HBV genome encodes seven proteins: HBx, core, polymerase, L-, M-, and S-HBsAg, and pre-core/HBeAg[9] (Table 1).

Epidemiology and Transmission

Patients infected with the HBV can transmit it to non-immune recipients who do not have hepatitis B surface antibody (are anti-HBs negative).[43] The mode of transmission may vary in different geographical areas.[44] In high prevalence areas, mother-to-neonate transmission is the predominant mode of transmission. To clarify here, the perinatal period is defined as beginning at 28 weeks of gestation and ending at 28 days after delivery. Therefore, the term "mother-to-neonate" is more specific in indicating peri- and postpartum transmission. In low-prevalence areas, the viral pool is maintained through sexual transmission between parents and subsequent mother-to-neonate transmission. In areas with intermediate prevalence, most infants get infected through horizontal transmission during early childhood.

Mother-to-neonate Transmission

Mothers can transmit the HBV to their fetuses *in utero* in 3–9% cases.[45,46] These infants do not respond to postnatal vaccination and/or administration of immunoglobulins. Hepatitis B virus has been detected in the villous capillary endothelial cells and trophoblasts of the placenta. The risk of transmission through this route can increase in the presence of high maternal viral load and preterm labor. The exact mechanism for prenatal transmission of HBV is not clearly known, but there are several possibilities as follows: (a) Transplacental leakage of HBeAg-positive maternal blood, if there is a disruption of the placental barrier;[47] (b) placental infection with trans-placental transmission;[45] (c) through infection in oocytes or spermatozoa, which can contain HBV DNA;[48] and (d) ascending vaginal secretions from an infected mother *in utero*.[45]

More than 90% of the cases of neonatal hepatitis B infections occur during the peripartum period.[49] Passive and active immunization of neonates born to HbsAg-positive mothers within 12 hours of birth can reduce the risk of HBV transmission by >95%.

Infants born to HBeAg positive mothers may remain at the risk of infection (9% rate of infection) with HBV even if they have received complete immunoprophylaxis and therefore they must be kept under close monitoring.[50] Those born to hepatitis B-infected mothers are at increased risk of acquiring the infection if the mother is HBeAg positive and/or has high levels of HBV DNA.[51] The infection is transmitted in 9–39% of highly viremic mothers despite postnatal vaccination (maternal DNA less than 10^5–10^6 IU/mL). In infants with borderline positive results, there may be a need for comprehensive evaluation as some may show altered HBsAg antigenicity.[52]

Table 1: Major structural components of HBV

Structure	*Available information*
Lipid envelope	The nucleocapsid is surrounded by a lipoprotein envelope derived from the nuclear membrane of the infected host cell.[25]
Glycoproteins	Projecting from the lipid envelope are viral glycoprotein spikes that bind specific host receptors to facilitate virus entry. Hepatitis B virus envelope has three viral surface glycoproteins—large, medium, and small proteins (LHBs, MHBs, and SHBs). Their expression is directed by the S gene including three start codons and one stop codon in a single ORF.[11,26]
Receptor-binding motifs	These are involved in virion attachment to cell surface receptors to allow the internalization of the virus particle. The primary target organ of HBV is hepatocytes, wherein HBV-BF, IL6, heparin sulfate, and lipoprotein lipase receptors have binding motif for preS1 region of HBV.[27,28]
Envelope protein	Hepatitis B virus particles are generated by budding of preformed cytoplasmic nucleocapsids into endoplasmic reticulum (ER) membranes containing the three viral envelope proteins (L, M, and S).[29]
Membrane protein	Either not expressed or relevance unclear fetal/infantile disease.
MHC or HLA proteins	Hepatitis B virus core antigen epitopes presented by HLA-A2 induce epitope-specific $CD8^+$ T-cell response.[30] Some MHC class II alleles have been found to confer protection against persistent HBV infection.[31]
Spike protein	Projecting from the lipid envelope are viral glycoprotein spikes that bind specific host receptors to facilitate virus entry.[32]
Surface tubules	During chronic infection HBsAg is expressed in large excess as non-infectious quasi-spherical particles and tubules that are about 22-nm diameter.[33]
Palisade layer	Either not expressed or relevance unclear fetal/infantile disease.
Viral tegument	Either not expressed or relevance unclear fetal/infantile disease.
Lateral bodies	Either not expressed or relevance unclear fetal/infantile disease.
Capsid	The capsid protein (Cp) packages the viral pgRNA and polymerase to form the HBV core.[34]
Capsomeres	The proteins that form the structural unit of the capsid may form three-dimensional structures known as capsomeres that are visible in an electron micrograph. The core proteins of the capsid bind the nucleic acid through a carboxy-terminal protamine region that contains nucleic acid-binding motifs organized into four repeats.[35]
Core membrane	Core membrane plays a role in nucleocapsid assembly as proven by a decrease in core membrane association coinciding with impaired nucleocapsid formation as a result of improper sorting and trafficking of core to assembly sites in Rab33B-knockdown cells.[36]
Protein core	The core (capsid) protein of HBV is the building block of nucleocapsids and mediates virus–host cell interactions in persistent HBV infections. It has a pleiotropic role in HBV replication, thereby making it an attractive target for antiviral therapies of chronic hepatitis B.[37]
Core fibrils	Either not expressed or relevance unclear fetal/infantile disease.
Matrix	The cytosolic matrix domain (MD) located between amino acids (AA) 103 and 124 of the large HBV envelope protein L is essential for virion formation.[38]
Enzymes	Hepatitis B virus polymerase is the best known enzyme in the HBV; has roles in protein-priming, RNA- and DNA-dependent DNA synthesis, and ribonuclease H activities.[39]
RNA elements	Hepatitis B virus replicates through an RNA intermediate. The pgRNA acts as a template for RT and also as a messenger RNA for core and polymerase. The pre-core RNA is involved in the translation of the pre-core gene product.[10,24]
Nucleus	Either not expressed or relevance unclear fetal/infantile disease.
Nucleosome	Either not expressed or relevance unclear fetal/infantile disease.
DNA	Hepatitis B virus has a partially double-stranded circular DNA genome of about 3.2 kb pairs.[40]
RNA	No RNA genome exists.
Genome-associated polyprotein	Either not expressed or relevance unclear fetal/infantile disease
DNA polymerase	HBV polymerase (P) protein is a four-domain multifunctional enzyme that has protein-priming, RNA- and DNA-dependent DNA synthesis (i.e., RT), and ribonuclease H activities.[41]
RNA polymerase	All known HBV RNAs, including the subgenomic, pregenomic, and precore RNA, are transcribed by cellular RNA polymerase II using cccDNA as the template.[10]
RT	Hepatitis B viruses (hepadnaviruses) replicate their DNA genomes by RT of an RNA intermediate.[42] The HBV RT has the unique ability to initiate viral DNA synthesis using itself as a protein primer in a novel protein priming reaction.[39]
Head	Either not expressed or relevance unclear fetal/infantile disease.
Base plate	Either not expressed or relevance unclear fetal/infantile disease.
Integrase	Either not expressed or relevance unclear fetal/infantile disease.
Tail	Either not expressed or relevance unclear fetal/infantile disease.
Tail fiber	Either not expressed or relevance unclear fetal/infantile disease.
Neck	Either not expressed or relevance unclear fetal/infantile disease.

The risk of transmission after amniocentesis and other diagnostic procedures during antenatal period is low and any procedure which is indicated for genetic invasive testing should not be withheld for the fear of transmission, especially when the mother is HBeAg negative with low HBV DNA load. Use of narrow gauze needles (22G) under supervision may possibly reduce the risk of transmission.[13]

The evidence for transmission with preterm rupture of membranes is uncertain, and hence, current recommendations do not suggest altering the obstetric management. Similarly, evidence for elective caesarean section to prevent the transmission is limited and is not routinely indicated for reducing the risk of transmission.[53]

Transmission through Human Milk Feeding

In neonates who are vaccinated and treated with the HBIg at birth, the chances of transmission of hepatitis B infection through breastmilk are markedly reduced.[54]

Paternal Transmission

Most of the transmissions from neonates born to HBsAg negative mothers. Infections from HBsAg positive fathers are considered to result from close postnatal contact of unprotected neonates with the infected blood and body fluids of the fathers.[55]

Clinical Presentation

The availability of vaccination and postexposure prophylaxis with HBIg has considerably reduced the risk of perinatal HBV transmission.[49] Infected neonates rarely present with biochemical or clinical signs of disease immediately after birth. They are usually asymptomatic but may develop mild, persistent liver enzyme elevations at 2–6 months of age due to chronic antigenemia (immune–tolerant phase).[56] The immune tolerant phase can persist for years and can then progress to the immune active phase.[57] A small proportion of neonates can develop acute hepatitis by 2 months of age and may present with fulminant acute hepatitis. Few may develop chronic liver disease and are at risk of cirrhosis and/or hepatocellular carcinoma.

Diagnosis

The diagnosis of hepatitis B infection in neonates, as in adults, is based on serological assays and detection of HBsAg.[58] Hepatitis B virus DNA is not recommended for screening since it may remain persistently high for decades even after clearance of HBV infection.[59] Apart from HBsAg, the detection of HBeAg, and antibodies to these viral proteins may also be useful for diagnosing the hepatitis disease in neonates. The presence of HBsAg in the infant at 1–2 months of age is indicative of vertical mother-to-infant transmission.[49] However, HBsAg can remain transiently positive in some neonates up to 21 days following hepatitis B vaccination.[60]

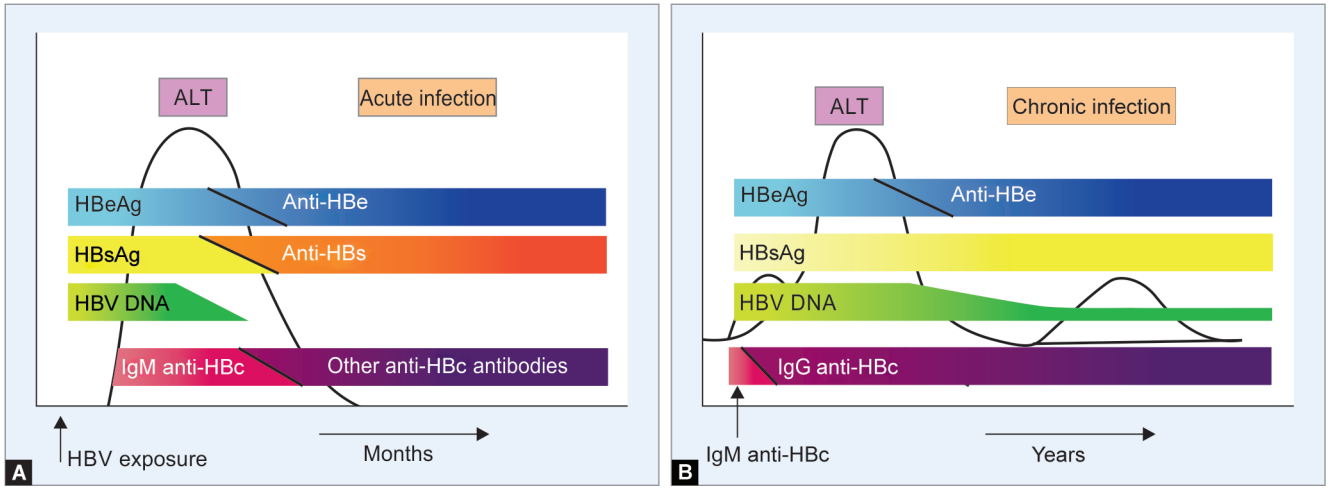
Differential Diagnosis

The differential diagnoses for elevated liver enzymes and acute liver failure presenting in neonatal period and infancy that should be kept in mind while evaluation include:[61]

- Congenital TORCHeS (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, and syphilis) infections;
- Rarely, vertically transmitted acute infectious causes seen chronically/seasonally in certain parts of the world (malaria, dengue, and chikungunya) may present with similar clinical features;
- Neonatal sepsis causing hepatitis and liver failure;
- Inborn errors of metabolism presenting with hepatic failure (tyrosinemia, galactosemia).

Postdiagnosis Evaluation

Once a neonate or infant is diagnosed to be infected with hepatitis B, serial follow-up with monitoring of liver enzyme activity and serological status needs to be done. The association of liver enzymes and phase of Hepatitis B infection is shown in Figure 2. A few cases may also require a liver biopsy in addition to the above tests to determine the response to treatment.[62] A few studies have shown histological changes, where the liver biopsy was repeated. Histopathological changes of chronic liver disease



Figs 2A and B: Acute HBV infections are marked by a period of transaminitis lasting for a few weeks. Anti-HBc, first IgM and then other subclasses can be detected for a few weeks. This is followed by serial appearance of HBV DNA, HBsAg, and then HBeAg that last for a few weeks and are then replaced by specific antibodies lasting for a few months

and early fibrosis may indicate predisposition to cirrhosis and hepatocellular carcinoma.

In chronic infections, transaminitis can last months to years. Also, IgG antibodies against HBc become detectable soon. Hepatitis B virus DNA and HBsAg remain measurable for prolonged periods extending into years. Both HBeAg and specific antibodies can also be detected for years.

Management

The management of neonates born to mothers with hepatitis B infections includes close follow-up and monitoring of serological status.[63] Most infected neonates are asymptomatic (immune–tolerant phase) and no specific management is required.[64] The immune–active phase can be associated with acute exacerbations with elevated liver enzymes and needs to be managed per standard protocol of acute liver failure management.[65]

Some of the infants in immune active phase can have persistently elevated liver enzymes along with raised HBV DNA levels.[66] In children older than 2 years, nucleoside analogues and interferon have been used off-label, but there is a need for evaluation of efficacy in neonates.[67] The goal of medical management in these cases is to reduce the risk of transmission, to and that of cirrhosis and hepatocellular carcinoma later in life. The selection of children for treatment is primarily based on phase of chronic HBV infection and it is suggested not to treat the patients in immune–tolerant phase, who have only mild elevations of ALT (<1.5–2 times higher than normal) and high HBV DNA levels (>20,000 IU/mL).[68] Treatment in this phase can reduce that rate of seroconversion, but it has also been associated with the development of drug resistance.

Children in immune–tolerant phase, particularly those with Asian heritage may not always show a consistent response to interferon.[69] Hepatitis B virus genotype B is seen more frequently in the Asian population, which may explain the suboptimal response to these drugs.[70] However, the reasons for these unpredictable responses are not well-elucidated. The preferred oral nucleoside analogues which have been licensed for use in United States are tenofovir, disoproxil fumarate and entecavir, in children above the age of 2 years.[71]

Duration of Treatment

(a) For children and adults with persistent HBeAg, indefinite treatment may be required; (b) In adults who undergo seroconversion and become HBeAg negative, treatment may be stopped though the optimal duration has not been defined. After completion of treatment, most centers follow these infants quarterly for at least 1 year to detect any flare-ups and exacerbations.[72]

Prevention

Mother-to-neonate transmission can occur *in utero*, at birth, or later in infancy. The risk of transmission without any use of active and passive immunization in peri- and postpartum period may approach 90%, but the universal maternal HBV screening, hepatitis B vaccination of newborn infants and use of HBIG prophylactically has reduced the transmission.[1,2]

In a large cohort study from the USA, the transmission risk was noted to be high when a mother was HBeAg positive, had a high HBV viral load of above 2000 IU/mL, or had received less than 3 doses of the hepatitis B vaccine.[73] The updated CDC guidelines (2018)[1] recommend the following for prevention of Hepatitis B infection in neonates:

- All stable infants weighing above 2000 gm should receive hepatitis B vaccination within 24 hours of birth;
- HBV DNA testing for all pregnant women infected with hepatitis B infection;
- Neonates born to women with HBV infection who do not respond to the primary vaccination series and continue to show anti-HBS titers above 10 mIU/mL, should be considered for single-dose revaccination.

Hepatitis B vaccination is the mainstay of preventing these infections.[74] Hepatitis B immunoglobulin can protect exposed infants for up to 3–6 months following perinatal exposure.[1] The presence of anti-HBsAg indicates immunity against HBV infection. Infants with vaccine-induced anti-HBsAg levels >10 mIU/mL are generally considered seroprotected. The three-dose hepatitis B vaccine series usually induces a protective antibody response (anti-HBS) >10 mIU/mL) in nearly 95% of healthy infants.[75]

The birth vaccine dose acts as postexposure prophylaxis for neonates born to HBV-infected mothers.[49,74,75] Hepatitis B vaccine and HBIg can prevent 75% and 71% perinatal transmission, respectively.[76] In combination, the efficacy approaches 94%. The two single-antigen vaccines approved for use in the United States and many other countries are Recombivax HB (Merck & Co., Inc., Whitehouse Station, New Jersey) and Engerix-B (GlaxoSmithKline Biologicals, Rixensart, Belgium). However, despite all approvals, currently available evidence is of very low-to-low quality, and we do not know with certainty whether antenatal HBIG administration has an effect on the proportion of newborns with HBsAg and HBV-DNA compared with no treatment[77] (Flowchart 1).

Revaccination

The HBsAg negative infants with anti-HBsAg levels below 10 mIU/mL should receive a single dose of the hepatitis B vaccine and then tested 1–2 months later for anti-HBS antibody levels.[1] Infants who still have titers below protective levels should be considered for a second 3-dose series of hepatitis B vaccination and then the titers should be measured 1–2 months later.[1]

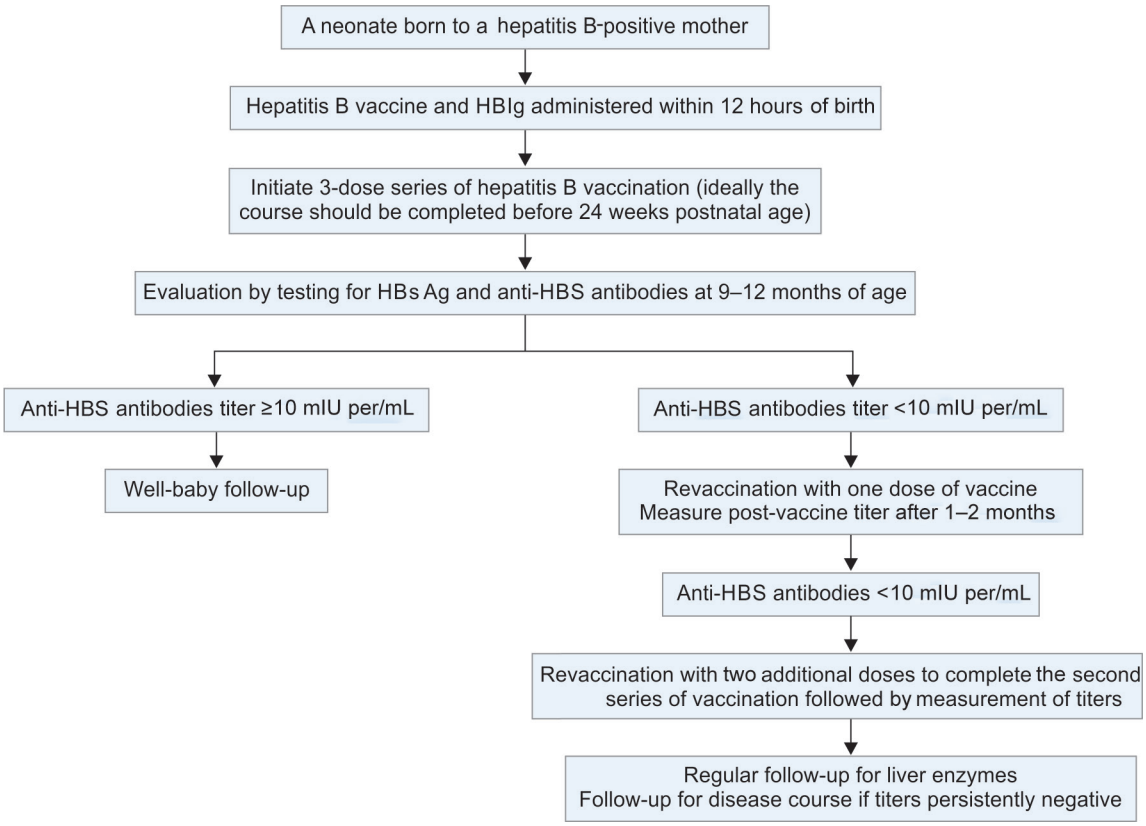
Maternal Antiviral Therapy for Preventing Perinatal HBV Transmission

All pregnant women irrespective of previous testing and vaccination status, should be tested for HBsAg during first trimester (WHO guidelines 2020).[78] Women who test positive for hepatitis B infections should be tested further for HBV DNA levels. In addition, they should be counselled about the concerns associated with hepatitis B infections and the need for antiviral prophylaxis/treatment for the neonate.

The WHO (2020) recommends that pregnant women who test positive for HBV infections with HBV DNA levels ≥ 5.3 $\log_{10}$ IU/mL (≥ 200,000 IU/mL) should receive tenofovir prophylaxis from the 28th week of pregnancy until at least the time of birth, to reduce the risk of transmission of the virus to the infant.[78,79] The systematic review commissioned by WHO on 129 studies indicated a protective effect regardless of the antiviral used for prevention (Tenofovir 300 mg: odds ratio [OR] 0.16, 95% confidence interval (CI): 0.10–0.26; lamivudine 100 mg: OR 0.17, 95% CI: 0.13–0.22; telbivudine 600 mg: OR 0.10, 95% CI: 0.08–0.13).[80]

WHO recommends that if antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for tenofovir prophylaxis, to prevent mother-to-child transmission of HBV.[80] The risk of

Flowchart 1: Management of neonates born to HBV-infected mothers



perinatal transmission is reduced drastically with timely initiation of treatment of affected pregnant women at 28–32 weeks with administration of Hepatitis B vaccine and HBIg immediately to the neonate immediately after delivery.[49] The drugs used in antenatal period are lamivudine and tenofovir, and due to lesser reports of resistance with tenofovir use, it is being preferred for maternal management of hepatitis B infection.[81]

Long-term Outcomes and Prognosis

The natural course of hepatitis B infections depends on the interplay between the viral antigen and the immune response. Perinatally-transmitted infections typically have a phase of immune–tolerance that may last for 10–30 years.[64] The infected individual usually remains clinically asymptomatic despite having high levels of HBV DNA, and the biochemical evidence of liver dysfunction remains low. The transition from an immune–tolerant to immune–active phase can happen years later, and then be associated with acute exacerbations or manifest as chronic failure.[69]

The rate of transition from acute to chronic phase is determined predominantly by age at infection and is approximately 90% for perinatally acquired infections, 20–50% for infections occurring between the ages of 1–5 years, and less than 5% for infections acquired during adulthood.[49,82] These findings underscore the importance of birth vaccination to prevent persistent infections with long-term liver dysfunction. Progression to the chronic state and cirrhosis predisposes to other complications and nephropathy, aplastic anemia, and hepatocellular carcinoma.[61]

There have been reports of spontaneous clearance of HbsAg.[83] In most of these infants, the clearance of HBsAg indicated good prognosis. The cumulative rate of spontaneous HBeAg clearance is estimated to be approximately 2% during the first 3 years and about 15% after 20 years of infection.[84] The low rate of viral clearance in adolescence and early adulthood accounts for the high frequency of maternal-infant transmission in Asian countries.[85]

The progression rates at different stages have been estimated as below:[86]

- Chronic hepatitis to cirrhosis – 12–20%;
- Compensated cirrhosis to hepatic decompensation – 20–23%;
- Compensated cirrhosis to HCC – 6–15%.

The cumulative survival rate for compensated cirrhosis is 85% at 5 years.[87] For decompensated cirrhosis, it is between 55% and 70% at 1 year and 14–35% at 5 years.

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