

Hepatitis B - Revised Recommendations

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📁 Nursing

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Objectives

1. Discuss the impact of Hepatitis B infections on healthcare and the diagnostic work-up of the patient infected with this virus.
2. Describe the different ways in which the Hepatitis B virus can be transmitted between adults and to children through perinatal transmission and breastfeeding.
3. Discuss the effectiveness of and recommendations for immunoprophylaxis against Hepatitis B and the potential treatment options for chronic infections.
4. Explain future concerns regarding the emergence of mutant strains of the hepatitis B virus.

Article

Hepatitis B Revised Recommendations

Authors: Mark D. Hennessy, M.D.

Objectives: Upon the completion of this CNE article, the reader will be able to:

1. Discuss the impact of Hepatitis B infections on healthcare and the diagnostic work-up of the patient infected with this virus.
2. Describe the different ways in which the Hepatitis B virus can be transmitted between adults and to children through perinatal transmission and breastfeeding.
3. Discuss the effectiveness of and recommendations for immunoprophylaxis against Hepatitis B and the potential treatment options for chronic infections.
4. Explain future concerns regarding the emergence of mutant strains of the hepatitis B virus.

Background and Healthcare Impact:

Hepatitis B was the first primary hepatitis virus discovered and reported upon in JAMA by Blumberg et al in 1965. Because the spread of this virus is primarily by a percutaneous or permucosal pathway, it was originally called serum hepatitis. Hepatitis B (HBV) is a circular DNA virus that is 42 nanometers in size. It is unique in that it is double stranded for two-thirds of its length and single stranded for the remaining third. It also contains its own DNA polymerase enzyme. None distinct subtypes exist. These are primarily important when performing epidemiology studies. All HBV particles contain a group-reactive determinant labeled "a" along with 2 sets of sub-determinants designated "d" or "y" and "w" or "r". The "w" was then found to have 4 different variants w₁, w₂, w₃, and w₄. Thus, eight

distinct subtypes have been identified, which are ayw₁, ayw₂, ayw₃, ayw₄, ayr, adw₂, adw₃, adw₄ and adr. With the boom of genetics in the past 10 to 20 years, hepatitis B has now been sequenced and there are 10 genotypes labeled A to J. Genotype A is the most prevalent in North America and Europe along with Genotype G; Genotypes B & C are dominant in Asia and Southeast Asia; Genotype D is more predominant in the Middle East; Genotype E is in Sub-Saharan Africa; Genotypes F & H are Central and South America; Genotype I is Southeast Asia; and Genotype J is mostly in Japan. It is important to know, however, that several Genotypes can be found in any given region around the world.

Many patients are at increased risk for being a chronic carrier of Hepatitis B. These include the ethnic groups of Asians, Eskimos, Pacific Islanders, Haitians, and Sub-Saharan Africans. Other risk factors include male homosexual activity, prostitution, intravenous drug usage, patients with multiple tattoos, prior blood transfusion recipients, hemodialysis patients, hemophiliacs or other patients with bleeding disorders, and individuals who work in hospitals or chronic care facilities.

At the present time, there are 350 to 400 million carriers worldwide. The carrier rate in the United States ranges between 0.1% and 1% depending upon the population tested (or from 1 in 100 to 1 in 1000 persons). Individuals who become chronically infected have a 10% to 25% chance of progressing to cirrhosis and a 200-fold increased risk for developing hepatocellular carcinoma.

If an adult becomes acutely infected, there is about a 10% chance of becoming a chronic carrier. This chronic carrier state can lead to the development of chronic persistent hepatitis, chronic active hepatitis, cirrhosis, or hepatocellular carcinoma, as stated above. Table 1 puts this information into better perspective.

Table 1: Significance of an acute HBV infection in the adult population

(Assuming 1000 Adults are infected)	
• Number with symptoms	250
• Number asymptomatic	750
• Number of fulminant cases (liver failure, DIC, etc.)	1 to 5
• Number who become chronic carriers	100
• Number who develop cirrhosis / hepatocellular carcinoma	15 to 25

Diagnosis:

The laboratory testing involved with Hepatitis B is one of the more difficult areas in understanding this infection. In the general laboratory evaluation, 6 distinct blood tests are available, which are:

1. Hepatitis B surface antigen (HBsAg) (originally called the Australia Antigen)
2. Antibody to hepatitis B surface antigen (anti-HBsAg)
3. Antibody to hepatitis B core antigen (anti-HBcAg)
4. Hepatitis B e antigen (HBeAg) and
5. Antibody to hepatitis B e antigen (anti-HBeAg).

6. Hepatitis B DNA viral load

The IgG antibody to the hepatitis B core antigen develops shortly after infection and usually remains positive for life. Some laboratories also offer an IgM antibody to the core antigen and this in conjunction with a positive HBsAg is more indicative of an acute HBV infection. The hepatitis B core antigen itself (HBcAg) is not available as a blood test. It is demonstrated primarily in liver biopsy specimens.

The other marker that develops shortly after infection is the presence of hepatitis B surface antigen or HBsAg and this remains positive until the patient becomes immune. If immunity occurs, then the antibody to the hepatitis B surface antigen or anti-HBsAg develops. There is a subset of the population that never produces an antibody to the surface antigen and these patients are considered to be chronically infected or are chronic carriers. The presence of an e antigen only signifies active viral replication and a more infectious disease state. The presence of antibody to the e antigen implies that the patient has a lower infectivity capability but does not exclude the possibility of transmission.

A patient who becomes immune to a hepatitis B infection will be positive for anti-HBcAg as well as anti-HBsAg. Over a long period of time, the antibody to the surface antigen may become non-detectable; whereas, the presence of the anti-HBcAg usually remains positive.

Patients who become chronic carriers will also have a positive anti-HBcAg, however, they never produce the anti-HBsAg. Instead, chronic carriers will continue to be HBsAg positive. Therefore, a positive IgG anti-HBcAg only denotes that an HBV infection occurred sometime in the past. The anti-HBcAg antibody is not protective and does not kill the virus. On the other hand, the anti-HBsAg antibody is protective and does result in immunity. A breakdown of the potential laboratory results is seen in Table 2 along with an explanation for the laboratory findings.

Table 2: The potential meaning of various Hepatitis B blood test results.

Possible Results	HBsAg	Anti-HBsAg	Anti-HBcAg	HBeAg	Anti-HBeAg
1.	+	-	-	-	-
2.	+	-	+	+	-
3.	+	-	+	-	+
4.	+	-	+	-	-
5.	-	-	+	-	+/-
6.	-	+	+	-	+/-
7.	-	+	-	-	-
8.	+	+	+	+/-	+/- *

1. Acute HBV infection (very early stages)** or chronic HBV carrier state (with low levels of non-detected anti-HBcAg).
2. Acute HBV infection** or chronic HBV carrier state (that is highly infectious).

3. Acute HBV infection** (later stages) or chronic HBV infection (lower infectious status, but still infectious).
4. Acute HBV infection** or chronic HBV infection (without HBeAg or Anti-HBeAg).***
5. Window state between the disappearance of HBsAg prior to the development of anti-HBsAg** or evidence of past HBV infection with a low level undetected anti-HBsAg.
6. Recovery from acute infection or infection in the remote past (now immune).
7. Infection in the remote past with a low level undetected anti-HBcAg or a person who is status post hepatitis B vaccination.
8. Late acute infection with early detection of antibodies (anti-HBsAg and anti-HBeAg) prior to the disappearance of the antigens, HBsAg and HBeAg, or a very rare unusual entity where the HBsAg is one serotype of the anti-HBsAg is for a different serotype.

* HBeAg and anti-HBeAg essentially never exist at the same time. However, the ability to detect antibodies has improved so much that this may occur transiently when a patient is developing anti-HBeAg as the HBeAg is disappearing.

** In this setting, an anti-HBcAg IgM antibody test might be helpful since a positive IgM denotes recent infection.

*** In some patients, HBeAg and anti-HBeAg never develop.

Transmission of HBV:

The transmission of hepatitis B is through a percutaneous or permucosal route. Therefore, transmission from person to person primarily occurs in the following ways:

- Through Blood or Blood Products
- Through IV Drug abuse
- Through contaminated or unsterilized needles (i.e. tattooing, ear-piercing, acupuncture, and needle sticks in the healthcare setting)
- Sexually
- Perinatal Transmission
- Contact through breaks in the skin or through mucus membranes (i.e. a splash in the eyes with contaminated fluid)

Hepatitis B surface antigen has been detected in all body fluids with the highest concentrations found in blood, saliva, and semen. Transmission of HBV through blood products at one time was a significant problem; however, now through the advent of testing donated blood, this risk is down to approximately 1 in 200,000 units transfused. The percutaneous spread is still significant in the IV drug abuse population and other exposures to potentially infected needles. This is due to the very high viral loads that are seen with this infection. For example, a high viral load for

someone infected with HIV or Hepatitis C (HCV) is at concentrations of 10^4 to 10^6 viral particles per ml of blood. In comparison, viral loads for Hepatitis B can reach levels of 10^{13} viral particles per ml of blood. Therefore, the risk of becoming infected following a needle stick exposure to HBV is much greater than the risk of becoming infected with HIV or HCV.

Sexual transmission is also significant when compared to other viral infections. Up to 40% of spouses will become infected after contact with a partner who has an acute infection. This rate is lower per contact if the partner is a chronic carrier; however, it increases based on the number of exposures. Perinatal transmission is a significant problem in parts of Asia and Sub-Saharan Africa and is a major concern because of the high rate of chronic carriers that develop. This is discussed further below.

With Hepatitis B, once infected the disease onset is slow and insidious. The first thing to appear (usually within 1 to 4 weeks) is the presence of HBsAg. This is followed by the development of anti-HBcAg. The elevation in liver function tests and the occurrence of clinical symptoms (including jaundice, dark urine, light colored stools, and right upper quadrant pain) can take 1 to 6 months to develop with an average of 2 to 3 months. The majority of patients (approximately 75%), however, do not have clinical symptoms that result in a diagnosis of hepatitis. Many of these will be asymptomatic or only have prodromal symptoms similar to that of the flu.

Vertical Transmission of HBV:

Vertical transmission of the hepatitis B virus from the mother to the neonate is a major concern. Studies have shown that up to 70% to 90% of neonates can become chronic carriers of the disease if they do not receive appropriate immunoprophylaxis following delivery, especially if the mother is HBeAg positive or has an acute infection in the third trimester. It is important to note that even if the HBsAg positive mother is HBeAg negative or even if she has a positive anti-HBeAg antibody, transmission to the neonate can still occur and immunoprophylaxis is indicated. A similar significance table is presented in Table 3. Note the differences in potential long-term outcome of a neonate infected with hepatitis B compared to that of an adult.

Table 3: Significance of an acute HBV infection in the newborn population

(Assuming 1000 Neonates are infected)

(Assuming an equal distribution of patients – HBeAg positive & negative)

• Number with symptoms	250
• Number asymptomatic	750
• Number of fulminant cases (liver failure, DIC, etc.)	1 to 5
• Number who become chronic carriers	600
• Number who develop cirrhosis / hepatocellular carcinoma	150

The transmission from the mother to the infant primarily occurs at the time of birth due to exposure to infected maternal blood or vaginal secretions. The recommended treatment of the newborn that is delivered of an HBsAg positive mother involves a dose of hepatitis B immune globulin (HBIG) followed by the hepatitis B vaccine series (given at birth, one month, and six months). If an infant receives this prophylaxis following delivery, the risk that the child will become a chronic carrier falls to about 5% to 10%.

Breastfeeding in a patient who is HBsAg positive is controversial. HBsAg has been found in breast milk in several studies; however, most of these have not shown an increase in the neonatal infection rate. It is of utmost importance, however, that these infants are adequately treated with both HBIG and the full vaccine protocol.

Several studies evaluated populations of pregnant women to determine the incidence of a positive HBsAg result. These studies found that only 50% of hepatitis B surface antigen positive mothers would be identified if screening were only performed for risk factors. Due to these studies, the Centers for Disease Control and the American College of Obstetricians and Gynecologists, recommended that routine prenatal blood test screening include the hepatitis B surface antigen blood test.

Since the development of the hepatitis B vaccine in 1982, the rate of acute hepatitis B viral infections in the United States has not changed. Epidemiology studies revealed that approximately 200,000 to 300,000 acute HBV infections occur in the United States each year. Perinatal hepatitis B infections only accounted for a small proportion of the total picture (approximately 20,000 cases). Research has shown that there is a significant incidence of child-to-child transmission of this virus. Therefore, the American Academy of Pediatrics and the Centers for Disease Control now recommend that all children receive the hepatitis B vaccine series in a hope that this will prevent future child-to-child transmissions and sexual transmissions and eventually decrease the rate of new cases in the United States.

Treatment:

Unfortunately, there is no certain cure for hepatitis B once a person becomes infected. The treatment of chronic carriers of Hepatitis B primarily consisted of interferon alpha-2b alone or in combination with other treatment modalities. This treatment was similar to the treatment of chronic Hepatitis C infected individuals. However, long-term effectiveness is seen in less than 50% of treated individuals. More recently, several new drugs (that are related to the research on HIV) have been developed and marketed. These are Lamivudine, Entecavir, Adefovir, Telbivudine, and Tenofovir. Many of these have been reported to drop a patient's DNA viral load to undetectable; however, resistance has developed along with reactivations (patients with a negative viral load that then turns positive again).

Overall, the best treatment approach for HBV is to prevent infection through the use of immunization. If a person is exposed to the virus through blood or sexual transmission, the treatment requires both hepatitis B immune globulin (HBIG) in conjunction with the hepatitis B vaccine. If a person wants to prevent a future risk of infection, the treatment primarily involves the hepatitis B vaccine series. One recent concern that has developed is the potential that some of the current testing for hepatitis B infection may not identify all of the mutant strains of hepatitis B that beginning to develop. Likewise, there is a concern that the vaccine might not cover all strains (mutants) in the future. However, for now, **Table 4** below depicts one approach to managing HBV immunoprophylaxis.

Because the risk of becoming infected and developing a chronic care status is much higher for a newborn exposed at the time of delivery, recent studies have looked at treating women prior to birth to lower the DNA viral load. These studies have involved small numbers and have usually used lamivudine, tenofovir, and telbivudine. Most recommend using a viral load cutoff value of a million (10^6); however, some have suggested a value of 200,000 IU/mL. In addition, no specific drug has been recommended as first line other than a suggestion of using tenofovir first, due to a lower rate of postpartum flare.

The immunogenicity of the hepatitis B vaccine is excellent with over 90% to 95% of the vaccinated population developing antibody to the hepatitis B surface antigen following the third injection. It is important to note that the site of vaccine injection is important. Adults should receive an intramuscular injection (IM) in the deltoid region. Intradermal injections and gluteal injections have resulted in lower response rates. For infants, an injection in the anterolateral thigh is preferable due to the smaller deltoid muscles.

The original vaccine, Heptavax, was created by purifying HBsAg from the blood of carriers. When a person is infected with HBV and is a chronic carrier, their blood contains the full virion, which consists of the core DNA encapsulated by the HBsAg surface protein material. In addition, their blood will contain millions of tubules and 22 nanometer spheres that consist of only the HBsAg protein. These spheres of HBsAg were purified to create the original vaccine. The vaccine was extremely safe because it went through a 3-step purification process of pepsin, urea, and formalin. However, the vaccine today is created in the laboratory through recombinant DNA in yeast, and therefore does not carry any risk for transmitting infection. The most common vaccines are Recombivax and Engerix-B, but others

are Elovav B, Genevac B, and Shanvac B. There is a Twinrix vaccine that immunizes for both Hepatitis A and Hepatitis B.

Table 4: Recommendations for Immunoprophylaxis of Hepatitis B

I. Perinatal Exposure:

Give 0.5 cc of HBIG at birth followed by 0.5 cc of the hepatitis B vaccine* within 7 days of birth (most now give the vaccine at the same time as HBIG in opposite anterolateral thighs). The vaccine is repeated at one month of age and at 6 months of age. Then check for HBsAg and anti-HBsAg at 12 to 15 months of age (the presence of HBsAg signifies treatment failure whereas the presence of anti-HBsAg signifies treatment success). If both are negative, a vaccine booster should be given.

II. Postexposure prophylaxis against a known HBV carrier – but the exposed individual has been vaccinated:

Check for the presence of anti-HBsAg and if positive, no treatment is indicated. If negative, give 0.06 cc/kg of HBIG single injection ASAP (but within 14 days) of contact along with a booster injection of the vaccine.

III. Postexposure prophylaxis from a known HBV carrier – but the exposed individual has not been vaccinated:

Give 0.06 cc/kg of HBIG single injection ASAP (but within 14 days) of contact and administer the vaccine series. Another option is to first draw blood from the exposed person for anti-HBcAg/anti-HBsAg and then give 0.06 cc/kg of HBIG single injection. If the test results are negative then administer the vaccine series, if positive, the exposed person was already previously infected, and the vaccine is not indicated.

IV. Postexposure prophylaxis from a known source with unknown HBsAg testing status – but the exposed individual has been vaccinated:

Test the source for HBsAg and the exposed person for anti-HBsAg. If the exposed individual is positive for anti-HBsAg, then no treatment is indicated. If the source is positive and the exposed person is negative for the antibody, give 0.06 cc/kg of HBIG single injection and administer a vaccine booster. If the source is HBsAg negative but the exposed individual is also negative for the antibody, only administer the vaccine booster.

V. Postexposure prophylaxis from a known source with unknown HBsAg testing status – and the exposed individual has not been vaccinated:

Test the source for HBsAg and the exposed person for anti-HBcAg/anti-HBsAg. If the source is HBsAg positive and the exposed individual is negative for the antibodies, give the exposed person 0.06 cc/kg of HBIG single injection and administer the vaccine series. If the source is HBsAg negative and the exposed individual is negative for the antibodies, then administer the vaccine series. If the exposed person is positive for the antibodies, then he or she was already previously infected, and the vaccine is not indicated.

VI. Postexposure prophylaxis from an unknown source – but the exposed individual has been vaccinated:

Test the exposed person for anti-HBsAg. If the test is positive for the antibody, then no treatment is indicated. If the test is negative for the antibody, administer a vaccine booster.

VII. Postexposure prophylaxis from an unknown source – and the exposed individual has not been vaccinated:

Test the exposed person for anti-HBcAg/anti-HBsAg. If the exposed individual is negative for the antibodies, administer the vaccine series. If the exposed individual is positive for the antibodies, then he or she was already previously infected, and the vaccine is not indicated.

* Hepatitis B vaccine doses for an infant and children under the age of 10, is generally 0.5 cc or half the adult dose.

The adult dose and children over the age of 10 is generally 1.0 cc. Heptavax comes at a concentration of 20ug of HBsAg per cc, Recombivax HB is 10ug of HBsAg per cc and Engerix-B is at a concentration of 20ug of HBsAg per cc.

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