



WGO Practice Guideline: Hepatitis B Vaccination

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1. Definition

Hepatitis B is a viral disease process caused by the Hepatitis B virus (HBV). The virus is endemic worldwide. The virus is shed in all body fluids by individuals with acute or chronic infection and by asymptomatic carriers, and is transmitted primarily by parenteral route such as blood transfusion or sharing needles. Oral transmission has a low efficiency. Sexual contact is a frequent cause. Healthcare workers are a high-risk group because of the risk of Needlestick Injury.

2. Epidemiology of Hepatitis B

Approximately 30% of the world's population, or about 2 billion people, have serological evidence of hepatitis B virus infection.

Of these, an estimated 350 million have chronic HBV infection and at least one million carriers die from liver cirrhosis and liver cancer each year.

The prevalence and incidence of HBV varies greatly in different areas of the world. The HBV virus is endemic worldwide with the areas of highest endemicity being China, Southeast Asia, sub-Saharan Africa, most Pacific Islands and the Amazon basin. In South America HBV is mostly not endemic. It is rare in children and more frequent in High Risk Groups.

In the developed world it is an illness affecting mostly high-risk adults, in the world's poorer areas it is highly endemic and widely present in children. Any vaccination programmes in those areas therefore are best focused on immunization in infants and children whereas in the western world it is better to focus vaccination on adults in high risk groups such as healthcare workers.

HBV infection leads to one of four outcomes:

- Fulminant hepatitis
- Recovery after acute infection
- Chronic carrier state
- Chronic Hepatitis B

The extent to which the outcome of HBV infection depends on immunological factors or on virus characteristics is uncertain. The age at which the infection occurs plays a very important role. In infants under 1 yr old, chronic infection will develop in 80-90% of cases; in children between 1-5 yr 30-50% will go on to develop chronic infection. By comparison, 30-50% of adults who become infected with HBV are symptomatic but only 2-6% of these adults develop chronic infection.

3. Risk groups and risk factors for HBV infection

Adult Risk groups for HBV infection

- Health care workers
- Policemen
- Migrant populations
- Frequent travellers
- Asylum seekers and refugees
- Military personnel
- Tourists
- Students
- Sex workers
- Injecting drug users
- Blood donors
- Hemodialysis patients
- Firemen
- Hemophiliacs

HBV transmission routes

HBV is transmitted through body fluids such as blood, saliva, semen, urine (breast milk is controversial).

The route can be :

- Perinatal (from mother to baby at birth)
- From child to child
- From unsafe injections and transfusions
 - Unsterile instruments, tattoo needles, dental equipment, other sharp objects
- Sexual contact
 - unprotected sex (whether heterosexual or homosexual)

HBV is transmitted through either skin puncture or mucosal contact with blood or other infectious body fluids. The virus is found in highest concentrations in blood and serous exudates.

Safe activities would include

- Hugging
- Shaking hands
- Preparing food
- Swimming in a pool

There is no evidence of a possible link between HBV vaccination and Multiple Sclerosis.

4. Diagnosis and Differential Diagnosis

The most common symptom of hepatitis infection is fatigue or tiredness. Fever, muscle and joint aches as well as nausea may also occur. Some people will notice that their urine becomes darker and their skin will show a yellowish tint (Jaundice) .

Principal symptoms

Fatigue and tiredness
Malaise
Jaundice
Fever
Muscle & Joint aches

Less common symptoms

Weight Loss
Depression
Anxiety, Irritability
Headaches
Sleep disturbance
Discomfort in the abdomen on the right side
Itching
Nausea
Appetite loss

HBV is one of 5 viruses known to cause hepatitis in humans (Hepatitis A, B, C, D, E) and the acute clinical illness caused by these viruses maybe similar. Specific diagnostic tests are required therefore to determine the cause in each case. Differential diagnoses include CMV, EB virus and Herpes virus.

Serological tests are available commercially for a variety of antigens and antibodies associated with HBV infection. HBeAg negative mutants are an important subset of patients.

For antigens:

- Hepatitis B surface antigen (HBsAg) for the presence of the virus
- Hepatitis B e antigen (HBeAg) correlates with viral replication and infectivity

For antibodies:

- Antibody to HBsAg (anti-HBs)

- Antibody to hepatitis B core antigen (anti-HBc); these antibodies to the core can be either IgM (acute) or IgG (chronic)
- Antibody to HBeAg (anti-HBe), indicating low infectivity and probably recovery

Other markers would be:

- HBV DNA = indicates virus presence
- DNA polymerase = determines the presence of HBV DNA
- HBsAg in liver cells = Orcein stain = Shikata cells = HBsAg inside hepatocytes

Serological markers of HBV infection vary depending on whether the infection is acute or chronic.

- A diagnosis of acute HBV infection can be made on the basis of the detection of IgM class antibody to hepatitis B core antigen (IgM anti HBc) in serum; IgM anti-HBc is generally detectable at the time of clinical onset and declines to subdetectable levels within 6 months. IgG anti-HBc persists indefinitely as a marker of past infection. Anti-HBs becomes detectable in patients who do not progress to chronic infection. The presence of anti-HBs after acute infection generally indicates recovery and immunity from reinfection.
- In patients with chronic HBV infection, both HBsAg and IgG anti-HBc remain persistently detectable, generally for life. In addition, a negative test for IgM anti-HBc together with a positive test for HBsAg in a serum specimen usually indicates that an individual has chronic HBV infection.

5. HBV vaccines and vaccination

Introduction

Since the discovery of HBV 35 years ago vaccination continues to be the best way for dealing with the condition, Hepatitis B is preventable and universal vaccination is probably best.

Two types of Hepatitis B vaccine are available.

- Recombinant or genetically engineered vaccines are made using HBsAg synthesized in yeast (*Saccharomyces cerevisiae*) or in mammalian cells into which the HBsAg gene has been inserted. Both consist of a suspension of HB surface antigen. Each country has different preparations.
- Human plasma-derived vaccines (PDV) are prepared from purified HBsAg from the plasma of persons with chronic HBV infection. There are more than 15 different PDVs licensed worldwide.

There are no significant differences in safety, immunogenicity or efficacy between these two types of vaccines

HBV vaccines will generate protective (>10 IU/ml) levels of antibodies to HBsAg in 95% of children and 90% of adults. . Re-vaccination works in 30-50% of persons who did not respond to primary vaccination. Revaccination of non-responders is not recommended after two series of vaccination (6 doses).

A distinction can be made between Pre-Exposure and Post-Exposure Vaccination

Pre-Exposure Vaccination

This is especially relevant in high risk groups.

The two available recombinant vaccines are similar in efficacy but dosing differs:

Recombivax-HB (10 µg of HBsAg)

Child < 11 yr HBsAg negative mother	2.5 µg
Child < 11 yr HBsAg positive mother	5 µg
Child 11-19	5 µg
Immunocompetent adult	10 µg
Immunosuppressed person	40 µg
Dialysis person	40 µg

Engerix-B (20 µg of HBsAg)

Child < 10 yr	10 µg
Child > 10 yr	20 µg
Adult	20 µg
Immunosuppressed person	40 µg
Dialysis person	40 µg

Post-Exposure Vaccination

A combination of Hepatitis B Immunoglobulin (HBIG) and HBV vaccine is recommended. This is of especial relevance in neonates where an immediate start of post exposure immunisation will prevent neonatal infection in infants of HBV infected mothers. It is important to vaccinate within 24 hours. There is no evidence of a protective effect if the vaccine is given > 7 days.

Direct exposure (percutaneous inoculation or transmucosal exposure) to HBsAg positive body fluid (eg NeedleStick Injury):

- HBIG single intramuscular dose of 0.06 ml/kg (as soon as possible)
- Followed by complete course of HBV vaccination (within 7 days)

Direct Exposure following sexual contact with a patient with HBV

- HBIG single intramuscular dose of 0.06 ml/kg (within 14 days)
- Followed by complete course of HBV vaccination

Contraindications & Sideeffects

There are very few contraindications.

- Severe allergic reaction to previous doses
- Severe allergic reaction to baker's yeast (as used in making bread), plasma-derived HBV vaccine can be used instead

- Fever >38.5°C

The following are **not** contraindications to administering HBV vaccine:

- Any minor illness such as respiratory tract infection or diarrhea with a temperature below 38.5°C
- Allergy or asthma
- Treatment with antibiotics
- HIV Infection, more information is, however, needed on the efficacy of HBV vaccination in neonates or infants that are infected with HIV.
- Breastfeeding
- History of seizures
- Chronic illnesses
- Stable neurological conditions
- Prematurity or low birthweight
- History of jaundice at birth
- Pregnancy

Vaccination Dosage & Schedule

Vaccination in infants, adolescents and adults involves a multistep process with the first two injections given one month apart and the 3rd one 6 months later.

Immunogenicity is 90% in immunocompetent adults but can be reduced by age. It is 85% in those over 40 yr and 75% in those over 60 yr of age. Vaccination in immunosuppressed patients is less effective. For example in patients with :

- HIV
- Chemotherapy
- Steroid use
- diabetes
- chronic renal disease
- cirrhosis
- smoking
- obesitas

Vaccination Route & Site

Infants:	intramuscular injection in the anterolateral aspect of the thigh
Older children:	intramuscular injection in the deltoid muscle
Adults:	intramuscular injection in the deltoid muscle

Injection equipment:

- 0.5 ml, 1.0 ml or >2.0 ml syringe
- 25 mm, 22 or 23 gauge needle

Vaccine Safety & Quality

Thermostability

- HBV vaccines should never be frozen. The freezing point of HBV vaccine is -0.5°C.
- HBV vaccine is stable for at least 4 years if stored between 2-8°C.

- HBV vaccines are relatively heat stable and have only a small loss of potency when stored for 2–6 months at a temperature of 37°C.

The Shake Test

If you see HBV vaccine frozen then it is damaged. However, a vaccine may also have been frozen earlier and then thawed again. The Shake test can be used to check if the vaccine has been damaged by earlier freezing.

- Compare the vaccine that you suspect has been frozen and thawed with vaccine from the same manufacturer that you are sure was never frozen.
- Shake the vaccine vials
- Look at the contents carefully
- Leave the vaccines to stand side by side for 15–30 minutes for any sediment to settle
- Do not use it if a sediment settles below an almost-clear liquid

6. HBV treatment

1. Treatment of acute HBV infection

A spontaneous recovery after acute infection with HBV occurs in 99% of previously healthy adults. Antiviral therapy is not likely therefore to improve the rate of recovery and is not required.

In fulminant hepatitis meticulous intensive care may improve survival. Orthotopic liver transplantation is the only proven therapy that improves patient outcomes.

2. Treatment of chronic HBV infection

Treatment of chronic HBV infection is difficult and limited in long-term efficacy.

There are three treatment options:

- Interferon- α monotherapy
- Lamivudine or other nucleoside analogue (lobucavir, famciclovir, adefovir, dipivoxil, entecavir)
- Combination therapies of interferon- α with a nucleoside analogue

A decision to treat must be based on a combination of

- serum liver tests (increased serum AST and ALT levels)
- virologic assays (presence of HBeAg or HBV DNA levels $>10^5$ copies/ml)
- liver histology (disease activity; fibrosis)
- virologic tests to exclude HCV, HDV, HIV

If the disease is inactive or mild it is best to do nothing and to monitor ALT levels.

If the disease is moderate to severe, treatment must be recommended.

When considering treatment, it is important to distinguish between HBeAg positive chronic Hepatitis B and HBeAg negative chronic Hepatitis B.

ALT levels can be used to decide whether or not to initiate therapy in patients with HBeAg positive chronic Hepatitis B.

An ALT level not exceeding 35 IU/l can be considered normal.

- | | |
|---------------------|-------------------------------------|
| 1. ALT level high | (more than 5 times the upper limit) |
| 2. ALT level medium | (2-5 times the upper level) |
| 3. ALT level low | (< 2 times the upper limit) |

Response rate to lamivudine and interferon- α is more than 50% in group 1, 20–35% in group 2. No therapy should be recommended for group 3.

Interferon- α therapy

HBeAg negative chronic Hepatitis B

- HBeAg negative chronic Hepatitis B is increasing. These are mostly patients infected with a virus containing a stop codon in the precore region. These patients are very resistant to treatment as they invariably relapse when treatment is stopped.
- Interferon- α therapy is not recommended for HBeAg negative chronic Hepatitis B (unless it is given for longer than 12 months)

HBeAg positive chronic Hepatitis B

- Interferon- α therapy recommended dose:
 - 5 Million Units (MU) daily or 10 MU 3 times weekly
 - 6 MU/m² 3 times weekly for children, subcutaneously, for 16 weeks (up to 32 weeks may be beneficial)

Advantages

- Short treatment duration
- No antiviral resistance (but precore mutants might be induced by previous interferon treatment)
- Excellent duration and quality of response

Disadvantages

- Expensive
- Side-effects (interferon treatment may be associated with flares – sometimes severe flares)
- Parenteral route less efficacy
- Decompensated liver disease

Contraindications

- psychiatric illness, in particular depression and suicidal tendency
- autoimmune or systemic disease
- severe leukopenia or thrombocytopenia

Note: do not use in patients with decompensated cirrhosis.

Pegylated Interferon

New forms of interferon are being developed in which the agent is covalently bound to polyethylene glycol (PEG). The interferon is slowly released as these covalent bonds degrade. Pegylated forms of interferon offer some advantages in ease of use. They can be

administered once a week only and they better meet the need for continuous circulating levels of interferon.

Lamivudine therapy

Long-term therapy with lamivudine is recommended for patients with advanced or decompensated chronic hepatitis B. Transplantation may become necessary because of deterioration in liver function, development of resistance or appearance of hepatocellular carcinoma (HCC).

Recommended dose:

100mg daily/oral

150 mg twice daily in HIV infected patients (and only in combination with other antiretrovirals)

Advantages

- Easy to administer and monitor
- Few side-effects
- Better response in selected groups (>30% eAg loss)
- Effective in subpopulations not responsive to IFN

Disadvantages

- Long-term durability of response not as good as for interferon- α
- Therapy often needs to be long-term (>12 months)
- Does not produce HBsAg loss
- Development of resistance
(Newer nucleosides against lamivudine resistant HBV strains include adefovir-dipivoxil, entecavir and FTC (fluorothiacytidine))

Combination therapy interferon- α + lamivudine

Combination therapies to date have not been more effective when compared with monotherapy (interferon or lamivudine alone). Combination studies with other nucleoside analogues may lead to better response and delayed development of resistance.

Recurrence of HBV after Liver transplantation

Both immune and antiviral therapies by themselves have limitations. HBIg by itself is associated with a recurrence rate of 20-50% in patients with HBeAg or high levels of HBV DNA. High doses of HBIg given intravenously are more effective than standard dosing but this is very expensive. Use of Lamivudine alone would be more convenient and economical but long-term efficacy is limited with recurrence rates of 25-30% in year 1.

7. Useful Websites

The American Association for the Study of Liver Diseases	www.aasld.org/
The Virus Hepatitis Network	www.hepnet.com
The American Liver Foundation	www.liverfoundation.org
American College of Gastroenterology	www.acg.gi.org

American Hepato-Pancreato-Biliary Association	www.ahpba.org
European Association for the Study of the Liver	www.easl.ch
International Liver Transplantation Society	www.ilts.org
Hepatitis Foundation International	www.hepfi.org/
The Viral Hepatitis Prevention Board	www.vhpb.org
SIGN (Safe Injection Global Network)	www.injectionsafety.org

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9. Queries and Feedback from you

INVITATION TO COMMENT

The Practice Guidelines Committee welcomes any comments and queries that readers may have. Do you feel we have neglected some aspects of the topic? Do you think that some procedures are associated with extra risk? Tell us about your own experience. You are welcome to click on the link below and let us know your views.

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