Comprehensive Guideline for

HEPATITIS B

People Awarness

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سرشناسنامه	علویان، موید، ۱۳۴۱
عنوان پدید آور	Comprehensive Guideline for HEPATITIS B People Awarness
مشخصات نشر	تهران:انتشارات شرکت سلامت پویان کوثر،۱۴۰۱=۲۰۲۲م.
مشخصات ظاهری	۹۶ص.: ۲۲×۲۹ س م.
شابک:	۹۷۸-۶۲۲-۹۴۶۱۴-۰-۲
وضعیت فهرست نویسی	فیپا
یادداشت	زبان: انگلیسی.
رده بندی کنگره	RC۸۴۸
رده بندی دیویی	۶۱۶/۳۶۲۳
شماره کتابخانه ملی	۸۸۴۱۹۱۳

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نام کتاب:	Comprehensive Guideline for HEPATITIS B People Awarness
ناشر:	انتشارات شرکت سلامت پویان کوثر
تألیف:	دکتر سید موید علویان
صفحه‌آرایی:	مهدیه کاظمی
طراحی جلد:	راضیه جانباز
تصویر سازی:	مریم نیما
نوبت چاپ:	اول
لیتوگرافی و چاپ:	چاپ کهن
شمارگان:	۱۰۰۰
شابک:	۹۷۸-۶۲۲-۹۴۶۱۴-۰-۲
قیمت:	۵۰۰۰۰۰ ریال

INTRODUCTION

Viral hepatitis is a widespread disease throughout the world and viral hepatitis B, in particular, is one of the most common type of this viral infection and a significant cause of hepatic insufficiency (liver failure) and cirrhosis. Resolving the problem of hepatitis requires increasing the level of awareness among all members of the society. Preventive measures necessitate attention to routes of transmission. Viral hepatitis B is not incompatible with living, marriage and family life. To comply with health advices, to avoid smoking, drinking, obesity and fatty foods are most important. Paying attention to medical advices regarding prevention and treatment will help in harnessing the disease. Fortunately, hepatitis B is a disease that can be put under control nowadays.

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2015 - Paris

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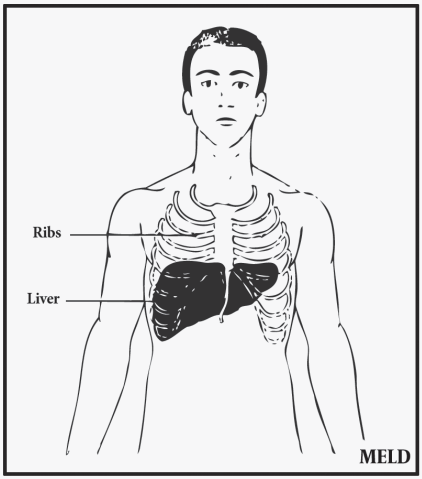
CHAPTER 01

Structure and Function of the Digestive System

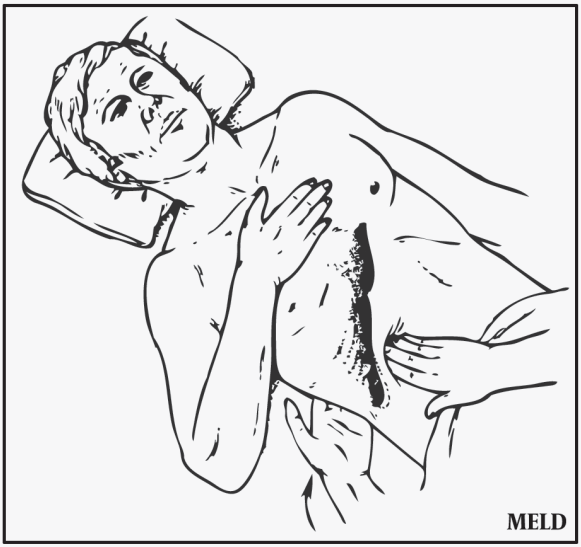
The digestive system has a hollow tubular form that begins from the mouth and ends in the anus. What we eat is first cut to pieces and ground in the mouth and then enters the stomach passing through the esophagus. Different parts of the digestive system help us in digesting the food by secreting various substances to prepare it for being absorbed in the intestines. Liver is a part of digestive system involved in digestion of food stuffs by what it secretes on them. It is located in the right upper quadrant of the abdomen and below the diaphragm.

Liver's structure and function.....

Liver is the largest gland in humans and can be compared to a chemical plant designed for producing, altering, storing and discharging different substance. It's location in the abdomen plays a significant role in its function. The liver is located in the right upper quadrant of the abdomen, behind the ribs and below the diaphragm. It weighs nearly 1500 grams in adult, which is one fiftieth of the total body weight. The liver has a rich blood supply that brings nutrients absorbed in intestines, directly to it. These substances are either stored in the liver or converted to chemicals that the body needs. The lower edge of the liver is palpable 1-2 centimeters below the



edge of ribs in the right side, during deep inspiration. This organ is normally protected by the ribs. It is consisted of liver cells, blood vessels and biliary ducts. The vascular plexus surrounding liver cells, transfers the digested and absorbed nutrients from intestines and store them. The secreted waste substances pour, through biliary tracts, into the gallbladder. The role of liver in metabolism of glucose and protein is very important. It also plays a significant role in digestion and absorption of fats, through production and secretion of bile. In addition, extraction of metabolic waste materials from blood and secreting them into the bile is performed by the liver. The produced bile is temporarily stored within gallbladder.



Q: Is it possible to detect liver diseases by examining the abdomen and palpating the liver?

No, the liver's edge is normally palpable during deep inspiration. It is worth mentioning that except in final stages of liver diseases, they are detectable through palpation of the liver and abdominal examination. Evidently, even by sonography it is not possible to diagnose liver diseases in all cases, and para-clinical findings will be necessary to ascertain the clinical diagnosis.

Liver's functions:

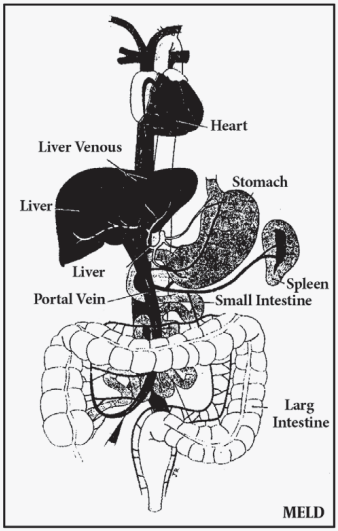
Liver is one of the largest internal organs and performs various vital functions in human body, the most important of which are mentioned below:

Upon entrance of food into the digestive tract, a series of different events occur to prepare it for use by the human body, namely entering the stomach, being mixed with the digestive juices and entering the small intestine, here, the food is

affected by chemical substances called enzymes, which are secreted by cells of small intestine's wall and also by pancreas, and prepared for being absorbed by intestinal cells. When absorbed, the nutrients pass into blood stream. These nutrients cannot be used directly by tissue cells, hence. They thereafter go to the liver to be changed to usable substances for all cells.

The role of liver in health

By making necessary changes in the absorbed nutrients and excreting toxic substances, liver plays the most Significant role in keeping us healthy. The most important of these changes include:



• Converting simple sugar (glucose) to its storable form (glycogen) and the reverse process when necessary, which play an important role in controlling the level of blood glucose.

• Converting the absorbed fat to absorbable and storable types for various cells of the body.

• Playing a major role in metabolism of protein (almost all proteins of blood plasma are produced by liver).

• Storing a number of vitamins (eg; A, B,…) and also some kind of metal (eg; iron, copper) to be used when needed.

• Destroying microorganism that enter the body through intestines. They first enter the liver in the bloodstream and it removes them by its defensive system.

The Role of Liver in Detoxification

Ammonium (NH_3) is a product of bodily chemical reactions, as well as intestinal bacterial flora, which is produced abundantly and enters the blood stream. It has detrimental effects on cells, especially brain cells, so the liver takes it up from the blood and, through a series of chemical reactions, converts it to urea, which is excreted by kidneys. The process of detoxification is not limited to ammonium a lot of harmful substances and drugs are also excreted from the body by the liver. When liver's function deteriorates, there will be an increase in the level of toxic wastes, including ammonium, which will have destructive effects on all parts of the body.

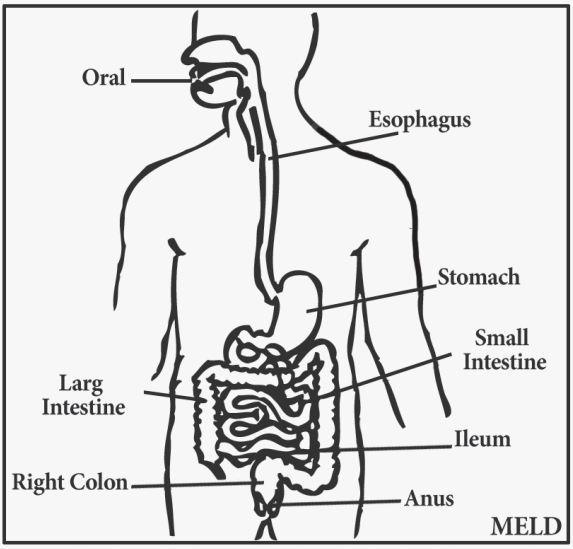
Q: Is it possible to live without a liver?

Considering the vital functions of the liver, it is surely not possible to live without it. However, in most liver diseases a small percentage of it is affected, hence only some of its functions will be out of order. Therefore, most liver diseases are not life threatening. In other words, if only one third of the liver remains functional all normal bodily needs will be met.

Protein production

Protein is one of the most important constituents of blood. Nearly two third of blood protein is albumin, which is produced solely by the liver. The average concentration of albumin in blood is 4 gr/dl. About 10 to 12 grams of protein is used by bodily cells and the same amount is produced by the liver. Indeed there is a balance between production and consumption albumin in our body. In cases of grave liver diseases like serious hepatitis or cirrhosis, the patient's serum protein decreases. Normal amounts of albumin in blood is an essen-

tial condition of health and proper blood circulation. For instance, decrease in albumin concentration results in swelling (edema) of different parts of the body (hands, feet, face). Other kinds of protein are also produced in the liver. These proteins are involved in blood coagulation (clotting) process and called coagulative factors; there are 31 of such proteins, 6 of which (factors 2, 5, 7,9,10 and 1) are produced in the liver. Their production requires presence of vitamin K. Hence, in cases of grave liver diseases or serious vitamin K deficiency, internal or subcutaneous bleedings easily occur. Other substances like transferrin are also produced in the liver, to transfer hormones within the body.



Bile production

Bile is a very bitter greenish yellow liquid produced constantly by liver cells, which is poured, through biliary ducts, into gallbladder, where it is concentrated and temporarily stored. Foodstuffs are first mixed with gastric juices in the stomach and then moves to the duodenum (the initial part of small intestine). Upon entrance of this mixture (chyme or chymus) into duodenum, bile is secreted from gallbladder and poured into duodenum. In a healthy adult, production and secretion of bile normally amounts to 500-1500 ml per day. This liquid mainly contains water, bilirubin and biliary salts that, in addition to excretion of bilirubin, helps in digestion and absorption of fats in intestines. Whenever the level of bilirubin increases in blood, jaundice occurs.

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CHAPTER 02

Viral hepatitis B From Microscope to diagnosis

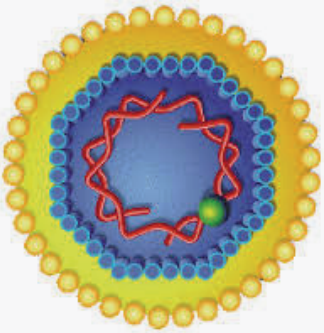
Hepatitis B virus (HBV) is the cause of hepatitis B infection in humans. This virus enters the liver and propagates there.

Substance produced by these viruses pour into blood stream. Form and structure of this virus are recognized using electron microscope. The virus to the hepadnaviridae family. Hepatitis B virus is a DNA virus with a very dense genetic structure.

Virology

The length of this virus is 24 nanometers (10^{-9} meters). The central part of the virus is the active one. The Australian antigen (surface antigen) is located on the surface of the virus. The complete form of the virus is called the Dane particle. It enters liver cell and make them to reproduce similar viruses. So that the cell's nucleus makes the active part of the virus, and other parts make small surface particles and additional proteins of the virus and put them around the Dane particle. Thereafter, the completed virus comes out of the cell and enters bloodstream. The contaminated person has these small surface particles (HBsAg) in his/her blood. Sensitive blood tests detect propagation of the virus in the body, the most sensitive of which is PCR that measures HBV's DNA. Now it has become possible to measure the quantity of the virus in blood and through these tests, performed by AMPLicor, Tack man or Real time technique, the method of treatment and follow-up of patients can be decided upon.

Hepatitis B virus



HBV propagates within liver cells and causes functional disorders in them. To infect a liver cell, it is essential for the virus to attach to its surface. After entering the cell, the virus moves toward the nucleus and begins propagation within it. HBs Ag

or HBV's surface antigen is then abundantly produced as 22 nanometer spherical and tubular particles that circulate in blood vessels. The body produces an anti HBsAg antibody to protect itself against these particles.

Viral Indicators

HBsAg is the most commonly used indicator to diagnose HBV infection. This antigen is found in acute and chronic infections. Anti-HBc Antibody is produced against HBc (core) antigen and indicates omission of HBV infection. HBV DNA test is necessary to confirm eradication of HBV infection. Unfortunately, its presence in certain condition is erroneously taken as a sign of hepatitis C infection, which has no relation to it.

HBeAg: Its presence in blood indicates infectivity of the virus. Although in recent years, following mutations in HBV, it is possible to have infective virus in absence of HBeAg.

HBV DNA: The serum level of HBV DNA is the most sensitive and important indicator of continuation or disruption of HBV'S propagation.

Q: What is hepatitis D (or Delta) VIRUS?

This incomplete virus needs Hepatitis B virus for its propagation. It is found along-with HBV in parts of Europe, Middle East, India and Africa. Detecting this virus is necessary in all patients with HBV and its treatment is very difficult.

Prevalence

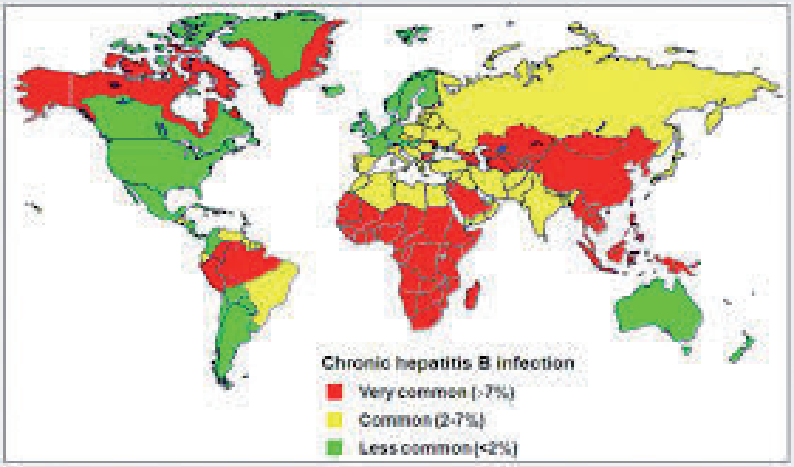
At the beginning of the third millennium, HBV is now one of the most common viral agents of disease, with more than 2 billion people exposed to it throughout the world and 350 to 400 million carriers. Fortunately, with campaigns for vaccination of neonates and high-risk people, the percentage (and not the number) of patients has decreased. The prevalence of chronic HBV infection varies in different parts of the world, hence the world has been divided into 3 regions:

Low Prevalence: the prevalence of HBV carriers in these region is less than 2%. These region include America, Western Europe, Australia and New Zealand.

Moderate Prevalence: In these regions, which include the Mediterranean, Japan, Central Asia, Middle-east, Eastern Europe and parts of Latin America, the prevalence of HBV carriers 2-8 %.

High Prevalence: The prevalence of HBV carriers in these region, which include South-East Asia, China. Pacific Island, Alaska and parts of Middle-East and Eastern Europe.

The difference among various regions in prevalence of HBV carriers is mainly due to the age of patients and patient's age has a reverse relation with chronicity of the disease.



Chronic hepatitis B is the third most common communicable infectious disease, after tuberculosis and malaria. On the whole, three fourth of world population live in high prevalence regions. Nearly 90% of HBV carriers live in developing or underdeveloped regions. The number of chronic carriers of HBV in China and Taiwan is 100millions and in America it is 1.2 million. In central parts of Africa the prevalence is very high and mainly due to transmission from mother to child and/or contamination of under 5 year old children.

On the basis of studies by Alavian et al. the prevalence of hepatitis B in Iran has decreased from 3.5-5 % in various regions of the country to 2% throughout Iran, most significantly due

MELD

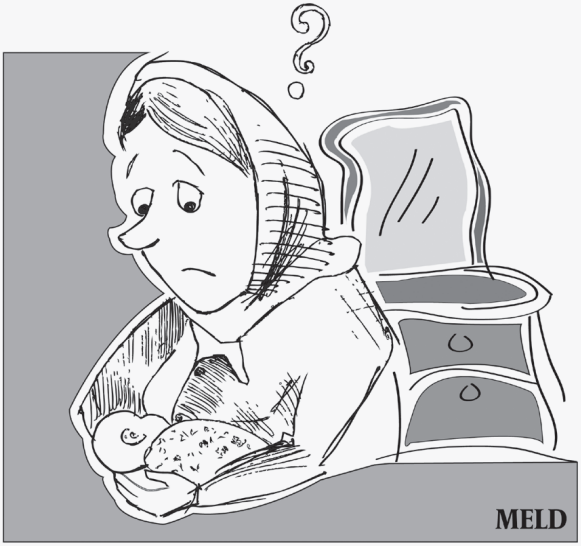
to vaccination of neonates, children and high risk persons. Currently, HBV is still communicated through contact with blood and blood products of infected subjects. The amount of HBV in blood is 100 to 1000 times more than other bodily secretions (e.g. Semen and saliva).

Routes of Transmission

The dominant route of transmission of HBV varies in different parts of the world. The latent phase of the disease, i.e.

from when the virus enters the body to appearance of sign &symptoms of the disease, has an average length of 45 days, which can extend to 160 days. The most important routes of transmission include:

- **Infected mother to child:** This has been the most important route of transmission in the past, so that after detecting a case of infection in a family, a significant number of sibling are also identified to be infected. The risk of maternal transmission of HBV has direct relation with the state of HBV's propagation in the effected mother. There is a higher risk of transmission in HBe Ag positive mothers or those with a high HBV viral load. Measuring the level of viral load during the last weeks of pregnancy, and anti-viral therapy if necessary. Will decrease the risk of transmission. It is very rare for unborn babies to get HBV from their mothers and in most cases transmission occurs during their birth. It should be noted that vaccination with hepatitis B vaccine and HBIG (Hepatitis B specific immunoglobulin can prevent neonatal contamination. There is no proof that caesarian section can prevent neonatal infection or breast feeding causes transmission of HBV to the infected mother's newborn baby.



Transmission of HBV from mother to child is called vertical transmission and unfortunately it is still important in countries where pregnant women are not tested for HBV infection or vaccination is not performed within the few hours after birth. Controlling this route of transmission promises a healthy future for the society.

- **Sexual transmission:** HBV is found in bodily secretions like saliva, semen and vaginal secretions. Unrestrained sexual behavior facilitates transmission of HBV. Vaccination against HBV can prevent transmission within the family. It is advisable for the infected mates to use condoms when one of

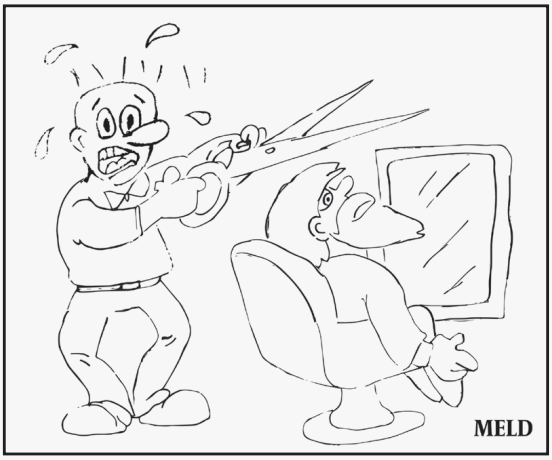
them has a genital ulcer. Sexual contact during the menses is prohibited and in cases of multi partner sexual relations using condoms is a must.

- **High risk blood contact:** Using syringes in common, transfusion of HBV contaminated blood, tattooing, ear piercing with contaminated tools, using contaminated toothbrush or razor, accidental puncture with contaminated needles in hospital staff, etc. are seen in many cases. Fortunately, the risk of transmission through blood transfusion is very low because of screening tests for HBV before using the donated blood.

- **High risk group include:** Hemophilia patients, dialysis patients, Health care personnel, injecting drug users, those with multiple sexual partners and family member of HBsAg positive patients.

- **Other routes of transmission include::** Acupunctures, organ transplantation, using non-hygienic dental care services, unhealthy cupping practice and in-family transmission.

In most Asian, African and middle-East countries, including Iran, transmission of HBV has occurred from infected mothers to their newborn children, however, even multiple extensive studies have not revealed the specific history of this infection. Unrestrained sexual behavior and injected drug abuse in western countries play an important role in transmission of HBV. Other common causes include using non hygienic dental care services, minor surgeries, practices like ear piercing, subcutaneous, injection, acupuncture, tattooing,



hair cutting and circumcision in non-hygienic conditions are considered significant factors.

Blood sucking insects such as mosquitos and bed bugs, especially in tropical areas can have a role in transmission, but there is no evidence of propagation of virus in their bodies. Piercing the skin with a needle for tattooing, in men on their body and in women on their face (eyebrow), is a known cause of contamination with infective agents.

HBV is resistant to heat, dryness and chemicals outside human body. This virus remains alive in.-20 c for 15 years, in room temperature up to 6 months and in a dry glass for 4 weeks, but in boiling water its life ends in 5 minutes. Chem-

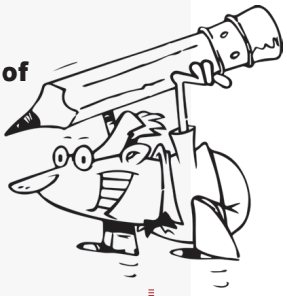
ical disinfectants like formalin, chloroform and glutar aldehyde kill it. To disinfect clothing and other contaminated objects, remove blood stains, then put the object in boiling water for 5 minutes or in chlorine solution (10 to 1) or other disinfectants for 30 minutes.

Hepatitis and in-family, transmission

When there is a HBV carrier in a family, transmission to other members of the family is possible, but requires long lasting contact and the virus will be transmitted through blood lasting contact. Although HBV is found in body liquids such as saliva, gingival groove secrections, urine and mothers milk, until now only blood and semen have been documented agent of transmission. However, there is also some evidence concerning transmission of HBV after being bitten by an infected person! It should be noted that in WHO reports only blood is known to be able to transmit HBV.

Theoretically, sneezing can convey contaminated drops of saliva from an infected person's mouth to the eyes of another person and cause infection, hence the mouth should be covered with a handkerchief when sneezing occurs. Albeit, vaccination against HBV can completely obviate the risk of in-family transmission.

Since the transmission of HBV occurs during the neonatal period, it is advisable to check other members of the family (including mother, father and siblings) of the patient.



The most important route of transmission of HBV include:

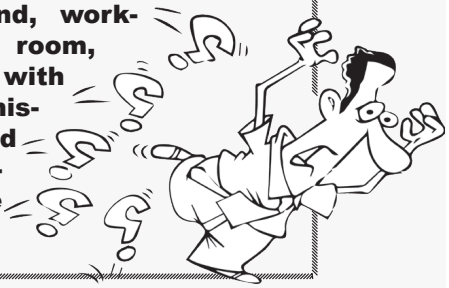
- **Mother to neonate**
- **Blood and blood products**
- **Contact with patient's blood (health care personnel)**
- **Tattooing and cupping in unhygienic conditions**
- **Injecting drug abuse**
- **Dental care using unhygienic instruments**
- **In-family transmission**
- **Insect bite (rare)**

Q:Can HBV be transmitted through every day contacts and encounters?

No,HBVisnottransmittedbysimpleeverydaycontactssuchasshakinghands,kissing,embracingasinplaceslikepools.

Q: Is it possible to get HBV just because of coworking with a HBs Ag positive person?

No, fortunately ordinary contacts like shaking hand, working in the same room, friendly relations with not cause transmission of HBV and observing hygienic rules will be enough.



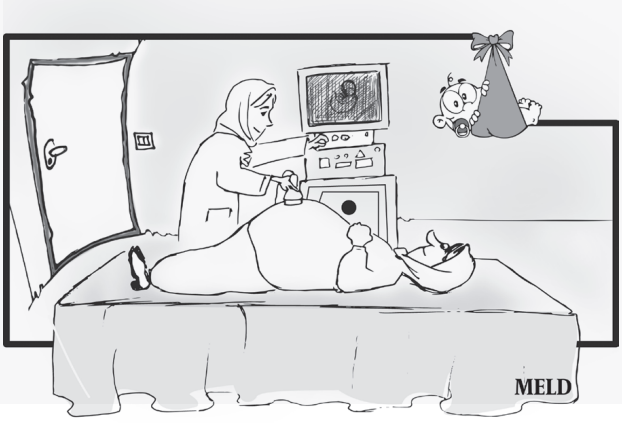
Ordinary contact with HBV carriers is not prohibited

Signs and symptoms

Hepatitis B can be either asymptomatic or with serious symptoms and severe involvement of the liver. Usually, when the viruses enter the body and after a period of latency, symptoms of common cold such as weakness, fatigue, indisposition, anorexia, fever, muscular pain, joint inflammation and skin rushes may appear. After a while the second phase begins with jaundice and obviation of early symptoms along with turbidity of urine or paling of stool. Then the patient enters the phase of convalescence. Children have usually milder symptoms or remain asymptomatic. A large number of patients do not show signs of jaundice or icterus, which may be to neonatal and childhood, mainly asymptomatic, infection with HBV.

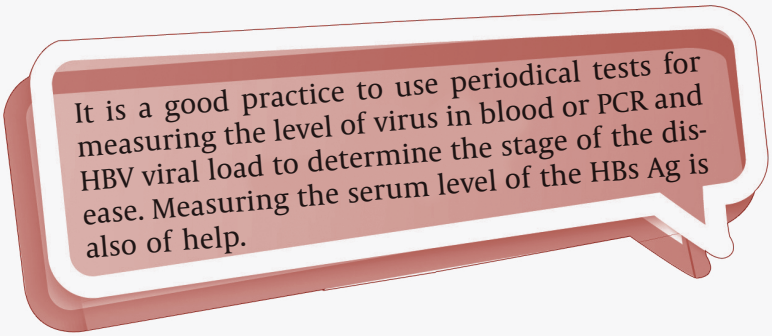
Diagnosis

Currently, there are proper tests that can confirm actual presence of the virus and establish the phase and status of the disease. In most cases, infection with HBV is diagnosed through blood donation or period's blood tests. Those infected are usually asymptomatic and become surprised about being infected. The most important diagnostic test for the disease is measuring HBs Ag. When someone is HBs Ag positive, this only means that HBV is present in his/her body. The patient's general disposition, liver's status (its size and results of specific liver test), sonography assessment and a few other tests regarding the activity of HBV in the body are the most significant diagnostic methods that help the physician in deciding for treatment of the disease. In the most patient s early abdominal sonographic is normal, however following aggravation and progression of the disease toward hepatic cirrhosis. The sign like splenomegaly, ascites and swelling in limbs, appear .In these are cases sonography will be of help.



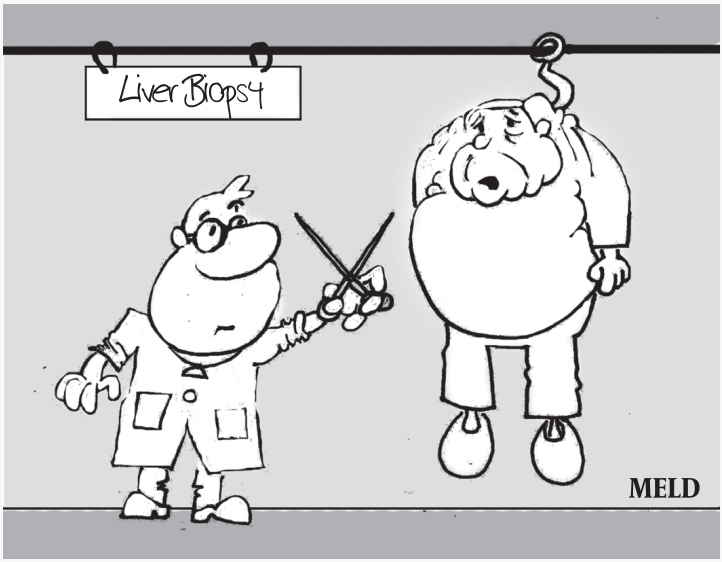
The Role of Hepatic Enzymes

Generally speaking, tests and measurements of hepatic enzymes can be useful in establishing the status of the disease. The more important hepatic enzymes include AST and ALT. The increased blood level of these enzymes indicate hepatic inflammation. The amount an a solute value of these enzymes have a weak correlation with severity of hepatic involvement.



The Role of Liver Biopsy in Diagnosis

One of the diagnostic methods to determine the level of liver damage is needle biopsy by sonography, which helps in recognizing the liver damage's severity and is used is choosing the best treatment. The resultant sample of liver tissue is examined by a pathologist.The first attempt for liver tissue sampling was made by Paul Ehrlich in 1883. During the Second World War, this method was used for research on viral hepatitis that had affricated the troops on both sides of the war.



Liver biopsy is an invasive method and must be performed by highly experienced personnel. The sample in this method consists of a few millimeter (up to centimeter) long piece of tissue to be examined in pathology lab. Using this method requires a short period of hospitalization of the patient along with clotting tests and hemoglobin concentration. Biopsy is a safe method in most cases. However, in very rare occasions there is a risk of bleeding that can be put under control by the performing physician. Abdominal pain, absence from workplace or mild shortness of breath are complications of liver biopsy. Currently, liver biopsy is performed in really necessary cases. Using this method in obese patients is very difficult and may become more complicated.

Fibroscan a modern diagnostic method

Using low frequency ultrasonic wave as a new technology for detecting the level of stiffness of the liver, which has a direct relation with liver fibrosis and permanent tissue damage, is a non-invasive method that can be used even for pregnant woman. A 4-point scale is used in grading the degree of liver fibrosis, form F0 to F4, which can also be used to grade the degree of liver stiffness, reported as KPa (Kilo Pascal). A complex software analyses the date of measuring the speed of wave and statistical formulas are used to determine the degree of permanent tissue damage (fibrosis). The procedure is completely painless. In liver biopsy only one in 50000 units of the organ is examined. While in Fibroscan one in 500 units of it is examined and this ratio reveals the higher accuracy of Fibroscan in detecting liver damages.

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CHAPTER 03

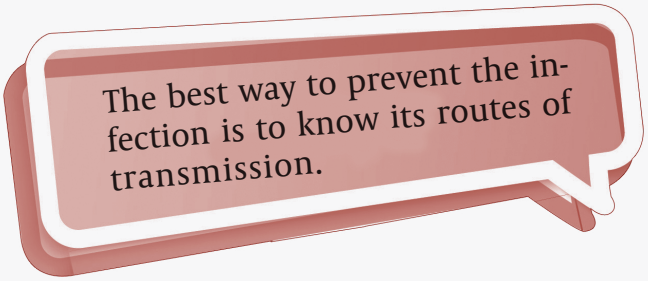
Hepatitis B Carrier

HBV can remain in latency for years and the infected person is known as hepatitis carrier. Carrier are those patients that HBV has remained in their bodies for more than 6 months, have a good general disposition and show no labratory detected liver dysfunction. In such situation, there is a peaceful coexistence of virus and its carrier, which causes no damage to the liver.

To confirm the liver's health, it is advised to perform Fibroscan and measure the blood level of HBV DNA.

Signs and symptoms in carriers

In most cases of infection, it is transmitted from infected mothers to their newborn babies. In some cases, following and acute viral hepatitis, the affected person becomes a carrier of the virus. In these patient, the signs and symptoms of hepatitis appears (e.g. anorexia, weakness, feebleness jaundice and dark yellow urine) but the immune system of the body cannot make HBs Ag negative, and after a period of six months, despite apparent wellness, the viral contamination remains behind. Some of these carriers may complain about reflux heartburn, anorexia and heaviness in the right side of their abdomen, which are not due to hepatitis. As mentioned earlier, HBV is present in blood and all secretions (e.g. saliva, sweat …) of these carriers and blood contacts with them can cause infection in healthy people. The virus has not been found in the stool of patients. Man is the sole reservoir of this virus and its transmission occurs human beings.



Q: Sometimes adults are infected with HBV, is it possible to cure them?

Yes, in acute cases the virus can be removed completely. In 5 to 10 percent of cases, the virus remains in the body, which results in carrier status. Until now, no certain causes have been found to make an acute hepatitis patient a carrier, but it seems that dysfunction of the immune system and type of virus may play a role in this regard. A familial predisposition may have a role in creating the HBV carrier status, which is not related to blood groups.

Q: One of my friends is afflicted with hepatitis B, can I go to his/her house for eating or not?

There is no prohibition in this regard, even if your friend cooks the food, you can eat it confidently! You do not even need to vaccinate against HBV for going to that friend's home or eating there.

HBV carriers should note that:

• They have to return to their doctor every six months for examinations and blood tests.

• When going to dentist, doctor, lab or other places where risk of transmission of the virus to others, inform them about being a HBV carrier.

• All members of a HBV carrier's family should be vaccinated against HBV. Alcohol consumption aggravates the disease, avoid drinking alcoholic beverages.

- Refrain from blood donation.
- Obese patients should try to lose some weight
- Never share personal items like toothbrush, towel, shaver, etc.

Treatment of carriers

A treatment for carriers is not yet available and since their hepatic function is not disturbed there is no need for treatment. Some kinds of drug therapy are done only for those affected with chronic hepatitis. Taking vitamins B_1 and D, as prescribed by a physician, can be useful. Avoiding obesity

and smoking as well as consuming more fruits and vegetable is recommended.

HBV carrier's fate

In most cases, there is no evidence of destruction or inflammation of liver cells and indeed some kind of adaptation and symbiosis has developed between the virus and the immune

Notice:

• HBV carriers can marry but their spouse should be vaccinated against the virus and the positive effect of vaccination must be confirmed. Thereafter, there will be no risk of transmission.

• Pregnant women should be tested for HBV infection in order to prevent its transmission to the newborn, if detected.

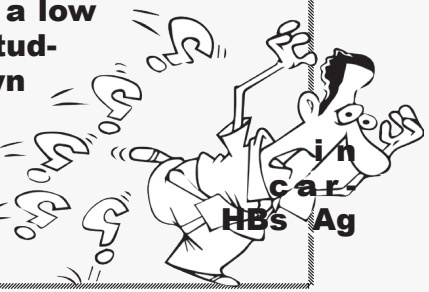
• It is better for HBV carrier women, if they have as many children as they want, to avoid repeated pregnancies.

• HBV carriers can live a normal life with no limitation for diet or physical exercise.

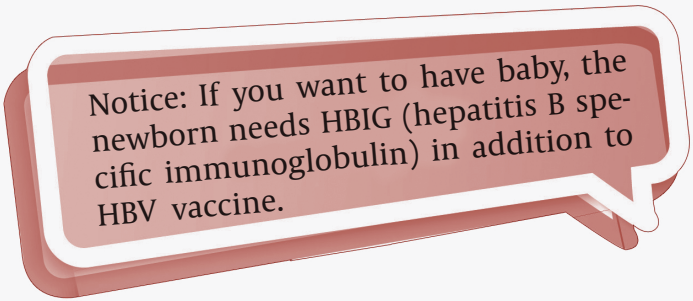
system, which may last for years and no liver disease appears. Sometimes, the virus remains latent during the patient's life time. Annually, one in every 100 carriers will become HBs Ag negative. However, 2 or 3 in every 100 carriers may experience a recurrence of the disease and reactivation of HBV in their bodies, sometimes years after the onset of the infection. Hence, HBV carriers are advised to have liver function test and physical examination every six months.

Q: Is it possible for a HBV carrier to become HBs Ag negative?

Yes, but with a low probability. Studies have shown that in 10 year only five in every 100 carriers become HBs Ag negative.



It is recommended for HBV carriers to have regular liver function tests (every 6 months) in order to detect early sings of chronicity and prevent further damage by appropriate treatment.



Acute hepatitis

Following infiltration of HBV into the body and a period of convalescence (needed for propagation of the virus and appearance of symptoms) from 4 to 42 week, early symptoms such as anorexia, nausea and vomiting, feebleness, headache, muscular pain, arthralgia, and fever appear. With the onset of jaundice, dark yellow urine and pale stool will diminish. Abdominal pains is also a symptom. Of the disease. Fortunately, in most cases and in less than 3 months there will be a decrease in jaundice and early symptoms disappear.

Chronic Hepatitis

As mentioned before, following a HBV infection, the virus may remain for years in a latent from in the body. In some cases, the virus may become active and cause liver inflammation. This may result in increased blood levels of hepatic

enzymes (AST and ALT) and appearance of clinical and laboratory signs of inflammatory liver disease.

Most patients with chronic hepatitis are asymptomatic, while in symptomatic ones, weakness, feebleness, fatigue and anorexia are the most common symptoms. A few percent of these patients have mild abdominal pain. With progression of the disease signs of hepatic cirrhosis begin to appear, it should be noted that a high level of viral load increases the risk of liver damage and even hepatic cancer. Controlling the virus, preventing fatty liver and avoiding alcohol are useful for these patients.

Hepatic Cirrhosis

Hepatic (Liver) cirrhosis includes a range of liver diseases with permanent damage to liver cells due to viral infections. Progressive liver fibrosis is a prelude to cirrhosis, or sluggishness of the liver, is a serious progressive disorder in response to damages to the liver due the chronic liver diseases which results in fibrosis or scar tissue. To better understand liver fibrosis, look at the scar of deep skin around with a thick layer of scar tissue. This tissue is made of collagen, which is produced by **Ito** cells in the liver that are normally inactive but become active for different reasons such as HBV. Signs and symptoms of cirrhosis vary depending on the disease and its intensity. These include: Weakness and fatigue, abdominal and limbs swelling, muscular weakness, skin darkening, ecchymosis, decrease in libido, nasal and gingival bleeding, breast enlargement in men and itching.

Definitive diagnosis of hepatic cirrhosis is made through using Fibroscan and liver biopsy as well as upper GI tract endoscopy to detect esophageal varices. In managing patients with hepatic cirrhosis, in addition to the underlying disease, i.e.; Hepatitis B, attention should be paid to complications and limbs swelling, controlling coagulate disorders by prescribing vitamin K, and improving bowel movement by lactulose are recommended. In some conditions, liver transplantations can be lifesaving. This procedure, usually using the liver of a brain dead patient, requires careful assessment on the basis of clinical and par-clinical criteria, as well as preparations on the receiving patient's side.

A Comprehensive Guide For Hepatitis B

CHAPTER 04

Treatment of hepatitis B

Before any discussion on treatment of hepatitis B and various antiviral medication used, a very important point to be mentioned is that determining the stage and intensity of the disease and factors like age, gender, duration of the disease, a family history of advanced liver disease or obesity, play an important role in decisions regarding to treat or not to treat and types of treatment. In some case not to treat the infected person along with dietary advices and observing requirements of personal hygiene, can be more useful than starting antiviral therapy. The main objectives of treatment are to control propagation of HBV and improving liver functions. Although in rare cases, there is a possibility of eradicating the infection. When HBV propagation is suppressed hepatic lesions will stop progressing. Follow up measures include test for ALT enzyme titer, HBV DNA in blood samples, HBe Ag and HBs Ag blood levels and, if necessary, liver biopsy and regular fibro scanning. Available medications include: alpha interferon or Peg interferon (Pegasus,) injection, and lamivudine, Adefovir, Entecavir or Tenefovir in oral forms.

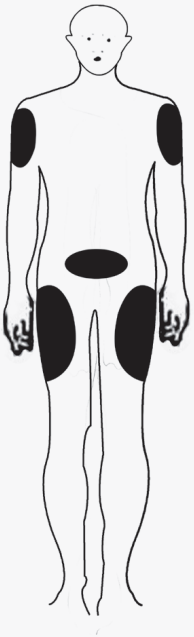
Alpha Interferon

Interferons are proteins with anti-viral and immune system regulating effects. These are produced by various cells in response to infections, including HBV infections. There are 3 types of interferon. Alpha interferon , produced by B lymphocytes and monocytes, beta interferon, produced by fibroblasts, and gamma interferon, produced by t-cell and natural killer helper cells. Among these, only alpha interferon has appropriate antiviral effects and is used in treatment of viral hepatitis. It controls and restrains propagation of HBV through stimulating the defensive system of the body. It seems that the body of patients with chronic hepatitis B is unable to secret enough amounts of interferon and there is an actual deficiency of interferon in these patients. Prescribing interferon for these patients aims to obviate this defect. Interferon in these patients aims to obviate this defect. Interferon in these patients will decrease HBV DNA (propagating virus), convert HBe Ag (less propagation) and return liver enzymes to normal levels. There are two kinds of alpha interferon: 2a and 2b, both used in treatment of chronic hepatitis.

Using alfa interferon will support the body in confronting viral infection and decrease propagation of the virus. It also invigorates certain white blood cell strains to detect virus infected cells in order to attack and destroy them.

Usage of Alpha Interferon

In cases where chronic hepatitis B is associated with deranged liver enzymes and high blood levels of HBV DNA alpha interferon may be used for treatment. Precise details of inflammation and destruction of liver tissue in liver biopsy or Fibroscan must be obtained, since in severe case of the disease using alpha interferon may be hazardous. Using alpha interferon in advanced stages of the disease, characterized by swelling and/or ascites, is not recommended. Alpha interferon has been marketed in two forms: conventional and polyethylene glycol bond (peg- interferon). The first form is used 5 to 10 million units per day or every other day, for one year. The latter is a newer and more potent form, called peg-interferon, which is used once weekly, with less complications but higher price. It is the result of attaching alpha interferon to polyethylene glycol, which is slowly released. Peg interferon is currently used in a weekly dose of 180 micrograms (for Pegasus). The same drug is used, along with ribavirin tablets, to treat hepatitis C. patients with hepatitis B should not take ribavirin.In some treatment protocols other oral antiviral drugs are used along with interferon. Alpha interferon is injected subcutaneously with a 45 angle. The figure below displays proper regions for injection, i.e. Muscles in arms and thighs.



Benefits and effectiveness of alpha-interferon

Alpha-interferon is preferred to oral antivirals in some patients because of the specified duration (12 months) of therapy and the fact that occurrence of mutations and resistance in HBV is nearly impossible. UN fortunately, just 30 to 40 percent of patients will respond to this long term treatment, and other remain unresponsive. Those groups of patients will have a better response to alpha-interferon include: those with high level of ALT, low level of HBV DNA, HBe Ag positives;

Points on using Alpha Interferon

• It should be injected subcutaneously with a 45 angle and intravenous injection must be strictly avoided.

• In order to decrease complications. Injections should be done at the evening.

• Interferon vials should be kept on the lower spaces of refrigerator. Prevent its freezing.

• After each injection, according to prescription, the remaining liquid should be thrown away.

• During the course of treatment drinking more water and similar liquids is recommended

• During treatment with interferon, some tests must be performed, refer to the designated medical center in due dates.

women; and those with a history of acute hepatitis. Using alpha-interferon in cirrhotic patients is forbidden, except in relevant research centers. Fortunately, most of those patients who respond to treatment, will remain for a long time.

Complication of alpha-interferon

Many drugs have complications in different patients and these complications can be diminished by certain method. Similarly, interferon has complications that are, fortunately, limited to the duration of treatment, with no long term effects. The most important complication is similar to influenza with fever and chills, headache, myalgia and arthralgia, fatigue and weakness, nausea and vomiting and sometimes diarrhea. They appear after hours following injection of alpha interferon and often disappear after a while. Within weeks after injection these complications become milder and will decrease through medication such as ibuprofen and acetaminophen. The intensity of complications varies in different patients. Other complications include: hair loss, irritability, depression and sleep disorders. Alpha-interferon affects the half-life of simultaneously taken medications with it and makes them remain in the body for a longer time. One example is theophylline (prescribed for respiratory diseases). Therefore, the physician should be informed about other drugs that are administered along with interferon.

Points on complications of using alpha-interferon

- Although loss of hair is a complication feared by many patients, it is not serious and even if it occurs, hairs will grow again after the treatment with alpha-interferon ends.

• If fever and chills persist for more than 2 weeks after alpha-interferon therapy, consult with your physician. It is not allowed to use this drug in patients with a history of attempted suicide or active psychological disorders. If a patient with depression being treated with anti-depressant drugs is going to take alpha-interferon, he/she should inform their physician in this regard.

• Inform your physician about such complications as drowsiness, convulsion, high blood pressure, and irregular heartbeat.

• Periodic tests and regular visits by your doctor are necessary during treatment with alpha-interferon.

Lamivudine

This is the first oral anti-viral medication against HBV, acting through inhibition of the enzyme responsible for propagation of the virus that results in decreasing the number of HBV in blood. Its use dates back to 1998 and has a better effect than interferon injection in short term. It has been used to inhibit HBV in children, cirrhotic patients, patient undergoing hemodialysis and kidney transplantation. Its daily dose is 100 mg in a single tablet. At first, it was said to be used for 2 years, but later it become evident that discontinuing lamivudine until resistance to it appears or, in rare cases, HBs Ag becomes negative, should not be attempted. In most cases it is impossible to discontinue the drug. Assume that you have a high blood pressure and

must take medication for it forever. Fortunately, lamivudine is not hazardous and rare complications such as abdominal pain, weakness and skin rushes may occur. One of its adverse effects is the high possibility of recurrence after discontinuation of it, as well as resistance to its effects following long term use. It is recommended to use periodic HBV DNA count and/or examining viral sequence and determining the possibility of resistance for early detection of resistance. When resistance to Lamivudine appears, its effectiveness will decrease and augmentation of hepatic lesions will be seen. It is recommended to use Lamivudine in combination with other antiviral medications. Currently, it is not advisable to begin treatment of HBV only with Lamivudine. Using more potent drugs will decrease the chance of occurrence of resistance. Those who have used Lamivudine to treat HBV, with no history of resistance to it, can continue its use. Avoid eating Lamivudine tablets along with fatty meals, since fat inhibits its absorption.

Adefovir

This is a nucleotidic analog of adenin. Its use in treatment of chronic HBV infections, even in cases resistance to Lamivu-

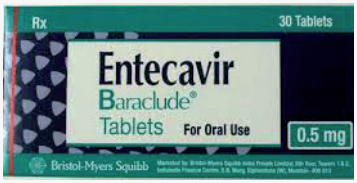
dine, is approved by many scientific circles. Adefovir is provided as 10mg tablets to be taken once a day. It will cause clinical amelioration and decrease HBV DNA count. Compared to Lamivudine the occurrence of resistance is less likely.

Its effects appear with delay and in 20% of cases there is an initial resistance to it. Periodic assessment of HBV DNA count is recommended. One of its adverse effects is renal complications that should be noted during the course of treatment. The patients are advised to refer periodically for functional tests and drink larger amounts of water every time they take Adefovir. Those HBV patients who have developed resistance to Lamivudine, it should be combined with Adefovir that decreases the chance of resistance to Adefovir. There are newer drugs also available.

Entecavir

This oral antiviral drug is an analog of Guanosine and more effective than lamivudine and adfovir. It can decrease blood HBV DNA rapidly. It should be mentioned that Entecavir is less effective in patients resistant to Lamivudine, hence it is

recommended to use larger amount of Entecavir in these patients. The initial dose is 5m.g although in patients resistant to lamivudine the dose is increased to 1mg. patients with renal problems will tolerate Entecavir better than other similar drugs. Although resistance to Entecavir is rare, it is reported in one percent of cases after 5 years of using the drug. Entecavir is well tolerated and its main adverse effects include: headache, respiratory infection, cough and abdominal pain.



Tenefovir

Tenefovir 's mechanism of action is similar to that of Lamivudine. It is a nucleoside analog inhibitor of reverse transcriptase enzyme that is effective against HBV and HIV. The daily dosage of 300mg (one tablet) is more effective than other antiviral drugs such as Lamivudine and Adefovir in diminishing HBV DNA count and normalizing hepatic enzymes (ALT).

Fortunately, no report of resistance to this drug, after 3 years of usage, has been received. The most common adverse effects include: headache, sore throat, backache, nausea and fatigue. In rare case, using Tenefovir results in renal complications, hence it is recommended to perform renal functional tests regularly (3 weeks to 6 months). In order to evaluate its effectiveness it is better to perform a quantitative assess-

ment of HBV DNA 12 weeks after the beginning of treatment with Tenefovir, and if no decrease (more than one logarithm) occurs, the patient should be considered as resistant to it, while decreasing HBV DNA signals a good response to treatment. HBV DNA test should be repeated every six months.

Conclusion

Management of HBV infection is a rapidly growing field and during the past 15 years, at least 5 new drugs have been marketed and 10 different drugs are currently being under-investigation. Using these drugs is associated with various complications and occurrence of resistance to them, but what should we do? In some cases, drug therapy is indicated, while in others no antiviral drug is used and only following hygienic and nutritional advice, along with controlling obesity and diabetes, will be required. Considering the law probability of eradication of HBV, patients should be prepared for long term, even lifelong, follow up of their disease.

A Comprehensive Guide For Hepatitis B

CHAPTER 05

Vaccination

In face of hazards of HBV infection for the society, the best way of prevention is to avoid high risk behavior, observing personal hygiene and vaccination against HBV.

Available vaccines are quite safe and effective in 95% of cases. The first type of HBV vaccines were prepared from carriers' plasma (i.e. containing purified HBs Ag and no virus) and was used in 1981. Later recombinant vaccine were produced using biotechnological procedures.

Q: Does using vaccines prepared from healthy carriers' blood or through other methods, result in HBV Infection?

-No, these vaccines are produced from HBs Ag of the virus and do not contain blood products or the virus, dead or alive, and are quite safe. There has been no report of transmissions of HBV through vaccination with hepatitis B vaccines.

Target groups for vaccination

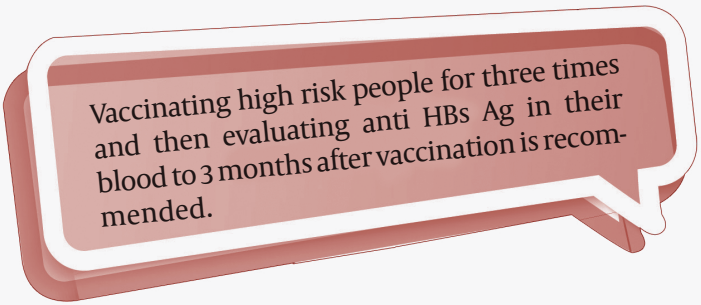
Target groups that should be vaccinated against HBV include:

- **All neonates**
- **Younger than 18 years old patients with a history of no response to hepatitis B vaccine.**
- **Health care personnel at risk of infection through needles or other contaminated devices, including physicians, surgeons nurses, Laboratories, blood banks and those who care for mental retarded patients at home.**

- **Spouse, children and parents of HBV carriers.**
- **Patients with frequent blood transfusions, eg. Hemophilia**
- **Patients, hemodialysis patient, thalassemia patients and injection drug abusers.**
- **Patients with chronic hepatic diseases and HCV infected persons.**
- **Those who have high risk sexual behaviors, especially STD patients.**
- **Inmates (prisoners) with high risk behaviors who will remain for more than 6 month in jail.**
- **Street cleaners, firemen, EMS personal, wardens, forensic lab and CSI staff.**
- **Organ transplantation candidates.**

Currently, there is a national campaign for vaccinating these target groups. Vaccination of neonates will be 97% effective in preventing the spread of HBV at large since the most important route of transmission consists of infected mother and her newborn. Various studies have revealed the fact that one third of the world population have been exposed to HBV during their life. That is the main reason for the advice

to vaccinate all populations, when and if feasible. However at risk population are to be in priority for vaccination. When this decision is made, the first priority includes students of high schools and universities. Neonates of HBs Ag positive mothers should receive both hepatitis vaccination and HBIG in different sites.



How to administer the vaccine

Hepatitis B vaccine is to be injected for adults in their arms muscles and for neonates in their thighs. Vaccination should be performed at 0, 1 and 6 months (3 times at 1 and 6 months after the first injection .The amount to be injected is 10 micrograms (one milliliter) in adults and 5 micrograms (0.5 milliliter) in neonates and children. Hepatitis B vaccine should not be injected in gluteal muscles, since its effect will be diminished.

The vaccine's effect

The vaccine should be kept at 2 to 8 , and must not be frozen , because freezing will obviate its effectiveness. Injecting the vaccine will stimulate specific lymphocytic immune cells (T-helpers) and produce a neutralizing antibody against HBs Ag. Using hepatitis B vaccine for three times will induce production of the neutralizing antibody against HBs Ag, i.e. making that person immune, in 95 percent of cases. Long term immunity against the disease depends on the degree of response to the vaccine by producing antibodies. It is recommended to measure the anti HBV anti body one to 2 months after completing the vaccination process. When the antibody response is higher than 10, the vaccinated person is immune to the disease. The best response will remain for years. Some conditions require measuring the antibody every 5 years. When measurement reveals a decrease of antibody to less than 10 IU, reinjection of the vaccine is recommended. Smoking, obesity, HIV infection, chronic diseases like renal failure and diabetes and freezing of the vaccine will decrease the immune response to vaccination.

IT IS RECOMMENDED THAT .....

- Injection of the vaccine be performed subcutaneously with a 45 degree angle. Strictly avoid intravenous injection.

- Hepatitis B vaccine and HBIG be injected for neonates of HBS Ag positive mothers on time and as soon as possible.

The vaccine's adverse effects

This vaccine has very mild adverse effects that occur only in one percent of cases as mild fever, burning, redness, pain and swelling at the injection site for one to two days after injection. Nearly one billion persons throughout the world have been vaccinated against HBV .The figure shows that vaccinating against HBV has no serious adverse effect. Its use is not contraindicated in pregnancy and lactation. Vaccinating those who are immune to or carrier of HBV (although not necessary) in not hazardous.

Q & A

Q: Is vaccinating HBV carriers against HBV useful?

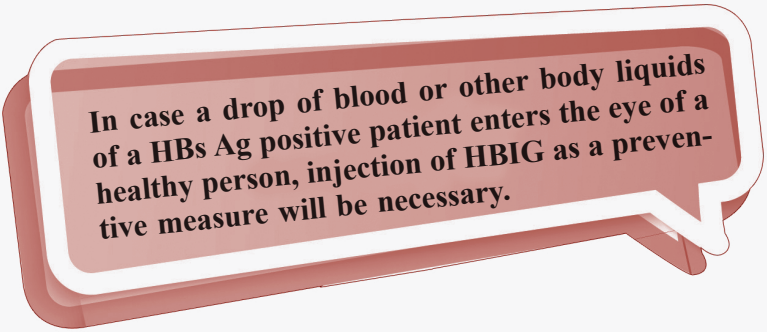
No, it is not either useful or harmful. Recently, scientists have been trying to produce a vaccine for HBV carriers, using genetic methods to extract certain parts of HBV, Which, after injection, stimulates their immune system to fight against HBV. Although using available vaccines for carriers is not advisable, when new vaccines are marketed they may use for this group of patients.

Q: Is necessary to perform HBs Ag test before vaccinating family members of HBV carriers against HBV?

Yes, unfortunately some patients get the vaccine before the test and then, following a blood test, find that they have HBV infection, and mistakenly think that vaccination has been the cause.

Q: I was injecting a vitamin B-complex vial for my HBs Ag positive mother when accidentally picked my finger with the contaminated needle, what is yours advise?

I hope that considering your mother's being a HBV carrier you have vaccinated yourself. Any way, it is recommended to go your physician as soon as possible (preferably in the first hour, utmost within 7 days) and if prescribed by him/her use HBIG. In case you are not vaccinated against HBV, start the process rapidly.



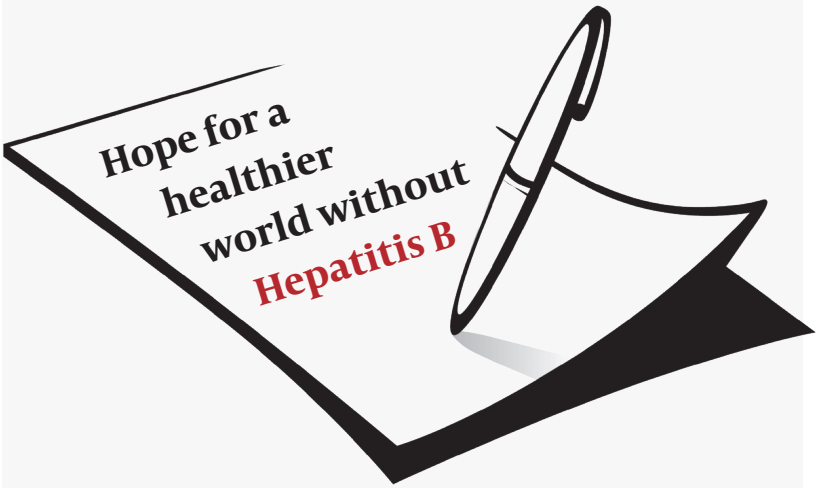
Q: Can a person with a history of hepatitis during childhood have vaccination after becoming an adult?

It is not prohibited to do so. Probably, there has been a type A hepatitis during childhood. After getting a negative result for HBV injection test, vaccination is allowable.

Q: Is there a need for repeating vaccination 5 years after completion of vaccination against HBV?

No , Recent studies have shown that in most cases , after a complete vaccination and positive anti HBV antibody , there is no need for repeating it up to 15 years later . However, measuring the antibody in high risk patients is recommended.


20mcg/mL
HEPATITIS B
VACCINE
(RECOMBINANT)
ENGERIX-B®
℞only
B
1 Adult Dose
GlaxoSmithKline


Hope for a
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