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Hepatitis B

Risks, prevention, and treatment

ELPA



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Dear Patient,

This booklet is intended to help you learn more about your illness and how to cope with it better. It is also intended to encourage you to maintain normal contact with other people and not to have unfounded fears about transmitting the disease. A further aim is to inform you more about how chronic hepatitis B affects your health and make you aware of possible treatments. We hope we are able to help you in this way. If you have any further questions, please contact in confidence the doctor in charge of your treatment.

A handwritten signature in black ink, appearing to read 'N. Piorkowsky'.

Nadine Piorkowsky
President, ELPA

A handwritten signature in black ink, appearing to read 'Stefan Zeuzem'.

Prof. Dr. Stefan Zeuzem
Scientific Advisory
Committee, ELPA

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Introduction

More than two billion people around the world have already had a hepatitis B infection. The WHO estimates that 400 million people are infected with hepatitis B.

Although an effective vaccination is available for hepatitis B, there are 10 to 13 million new infections every year. In the final stage of the disease, chronic hepatitis B can lead to liver cirrhosis and liver cancer. About one million people die every year as a result of hepatitis B.

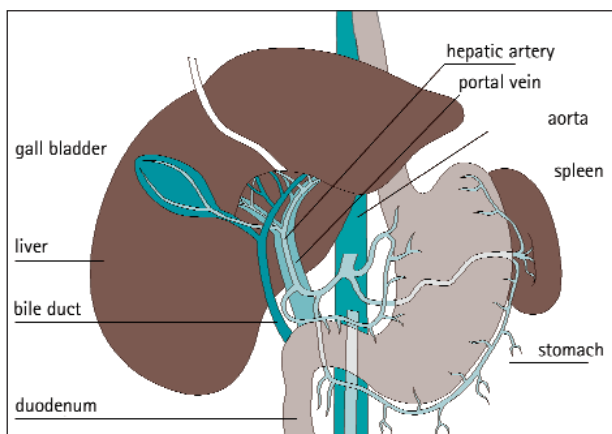
An effective vaccination is available. The treatment for people who are already chronically infected is being continuously improved.

The liver

The liver weighs approximately 1,500 g and is the largest internal organ in the human body. It is located in the upper right abdomen and is encapsulated in connective tissue.

The liver is the body's central metabolic organ. Its tasks include breaking down toxins that have entered the body through the intestines before they can reach the primary circulation. Nutrients entering the liver via the intestines are processed here. The liver produces key proteins needed for tasks such as blood clotting and warding off infection. Another important function is the production of bile, which travels to the duodenum through a special system of ducts. The bile removes waste matter from the red blood cells and facilitates the digestion of fats. Various toxins are also excreted from the body via the bile.

The liver itself has no nerve fibers to transmit pain. However, pain may be caused by tension in the connective tissue enclosing the liver when the liver swells or develops scarring as a result of inflammatory processes.



Location of the liver in the upper abdomen and its blood supply. The nutrient-carrying blood from the intestine reaches the liver through the portal vein.

Viral hepatitis B

Hepatitis B infection is infection of the liver with the hepatitis B virus (HBV). In most cases (>90% of patients) the body self-heals after acute hepatitis B infection. Many patients recover from infection with the virus without noticing it. However, in less than 10% of infected patients, the body's immune system is unable to deal with the virus. Patients whose illness persists for longer than six months are said to have chronic hepatitis B.

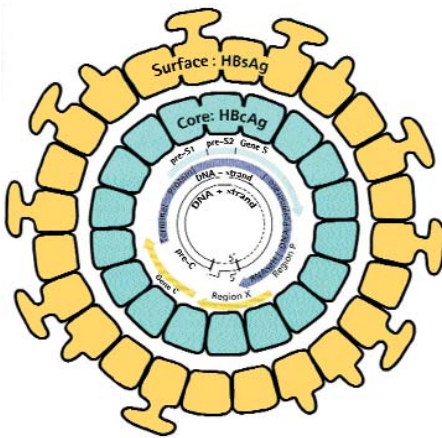
The clinical manifestations and outcome of chronic hepatitis B depend on the amount of the virus in the body and on the strength of the patient's immune system. The degree of hepatitis activity can be gauged on the basis of certain viral components in the blood, the antibodies produced by the human body in response to these virus components, and other lab markers (Table).

HBs Antigen	Virus component in the virus envelope; a sign of acute or chronic hepatitis B
HBe Antigen	Virus component detected in the blood. Indirect evidence of virus multiplication (replication)
HBc Antigen	An element of the virus capsule. May be detected in the liver but not in the blood
Antibodies (anti-HBs, anti-HBe, anti-HBc)	Produced by the body's immune system to remove the virus from the body
HBV DNA	Genetic material from the hepatitis B virus (deoxyribonucleic acid)
Transaminases	Liver enzymes (ALT, AST) indicating increased inflammatory activity in the liver
Histology	Microscopic examination of tissue (e.g. from the liver)

Table: Important tests for hepatitis B. Antigens (Ag) are substances which the body identifies as foreign (e.g. virus components) and which lead to the production of antibodies (Ab).

Some forms of chronic hepatitis B produce only small amounts of the virus in the body (low-replicative chronic hepatitis B). Other forms of the disease produce the virus in very large amounts (high-replicative chronic hepatitis B). Low-replicative chronic hepatitis B is not usually associated with rapid disease progression. Most patients have normal results in liver function tests. HBs antigen can be identified in their blood, but HBe antigen is not usually

detected. Patients with high-replicative chronic hepatitis B have more than 100,000 virus copies per mL of blood (corresponding to approx. 20,000 IU/mL). HBe antigen may be detected as well as HBs antigen. However, HBe antigen is not detected in many patients (approx. 50 %) with high-replicative chronic hepatitis B.



Model of the hepatitis B virus

The type of chronic hepatitis B in a particular patient can be identified on the basis of blood tests. The antigens and antibodies in the blood, the amount of viruses in the blood (viral load), liver function tests (enzyme levels), and histology tests on liver tissue tell the doctor more about the level of hepatitis activity.

Symptoms of hepatitis B

Between six weeks and four months after infection with hepatitis B viruses (incubation period), some patients experience flu-like symptoms, joint aches and fatigue. Not all patients develop the "typical" symptoms of severe liver disease such as jaundice with discolored stools and brown urine, and upper abdominal pain. Around two-thirds of patients with acute hepatitis B experience few symptoms, if any.

The symptoms of chronic hepatitis B are usually even less apparent. Some patients feel very tired or experience right-sided upper abdominal pain, and many do not notice their disease at all.

Mechanism of disease

In patients with chronic infection, the hepatitis viruses keep infecting more and more liver cells. The infected liver cells degenerate and are replaced by new liver cells. White blood cells migrate into the liver tissue as a sign of inflammation. The white blood cells ensure that infected and dead liver cells are destroyed and cleared away, but are usually powerless to remove the virus itself. The dead liver cells may later be replaced by connective tissue (scar tissue). When connective tissue starts forming in the liver, the early stage in the process is called hepatic fibrosis and the late stage is called cirrhosis. Connective tissue can be broken down, at least in part, if chronic hepatitis B is successfully treated.

Transmission

The hepatitis B virus is usually transmitted via infected blood, sexual contact, or during labor. The hepatitis B virus is much more contagious than, say, the AIDS virus (HIV) or the hepatitis C virus. Hepatitis B virus is only transmitted from human to human.

Sexual transmission

Unlike hepatitis C, hepatitis B is commonly transmitted by sexual contact. Patients with detectable levels of virus in their blood should use condoms to protect their partners. Hepatitis B may also be transmitted in the saliva and other body fluids. Therefore, vaccination of the sexual partner is important.

Transmission via blood

The hepatitis B virus may be transmitted via blood or blood products. The modern test methods used today to screen blood are highly sensitive, and the risk of transmission by this route is very slight as a result. The virus may also be transmitted through the use of dirty syringes or needles. Risk factors for contracting hepatitis B therefore include drug use, tattoos and body piercing. Transmission of the hepatitis B virus via open wounds, razor blades and toothbrushes is also possible.

Infection in newborn babies

The risk of infection in a newborn baby whose mother has hepatitis B virus infection is greatest during or shortly after birth. The risk of virus transmission during delivery ranges from 10% (low-replicative chronic hepatitis B) to almost 100% (high-replicative chronic hepatitis B). Therefore, babies born to a mother with hepatitis B virus infection must always receive active and passive immunoprophylaxis immediately after birth (simultaneous vaccination and administration of immunoglobulin).

Opinions differ as to whether hepatitis B infection can be transmitted by breastfeeding. The likelihood of virus transmission during breastfeeding seems to be related to the mother's viral load.

Complications of hepatitis B

Patients with chronic hepatitis B have a significantly higher risk of developing cirrhosis in subsequent decades. The risk of developing cirrhosis depends among other things on disease activity and disease duration. Factors which may accelerate the development of cirrhosis include other chronic liver diseases, e.g. with other hepatitis viruses (e.g., co-infection with hepatitis C virus) and exposure to substances that damage the liver. The main culprit is alcohol. Cirrhosis is defined as a state in which a large part of the liver tissue has been replaced by connective tissue. This destroys the normal liver tissue structure and affects the blood supply, causing high blood pressure in the portal vein (the vein between the intestine and liver). Backflow of blood may cause dilated veins (varices) to develop in the esophagus (food tube) and stomach. If these veins burst, severe gastrointestinal bleeding may occur. The risk of bleeding is increased by the fact that the blood's ability to clot is impaired by the reduced synthesis of protein in the liver and a reduction in the number of blood platelets.

Accumulation of body fluids (ascites) in the abdominal cavity may occur, one reason being the high blood pressure to the liver.

If cirrhosis is present, the liver may be unable to break down some of the toxins entering the blood from the gastrointestinal tract, allowing these toxins to enter the main circulation. These toxins may cause increased fatigue and poor concentration (hepatic encephalopathy [encephalon = brain]).

Reduced protein production in the cirrhotic liver impairs blood coagulation and results in an undersupply of sub-

stances needed by the immune system. As a result, the patient is more prone to infections.

Retention of bile in patients with severe liver disease commonly causes yellowness of the eyes and skin (jaundice). This may be accompanied by itching. Dark urine may be produced.

Patients with a long history of chronic hepatitis B are also at greater risk of developing liver cancer (hepatocellular carcinoma). The risk seems to be greatest for patients with a high viral load (HBV-DNA). In most cases the hepatocellular carcinoma is secondary to cirrhosis, but there are reports of liver cancer occurring in patients with chronic hepatitis B who had no history of cirrhosis. Patients with low-replicative chronic hepatitis B (HBs antigen carriers) are also at greater risk of developing liver cancer. Therefore, these patients also require regular ultrasound scans and blood tests for monitoring purposes. In some patients, chronic hepatitis B is severe enough to warrant a liver transplant.

Hepatitis D

Hepatitis D is another viral disease of the liver. It is triggered by the hepatitis D virus. Hepatitis D can only occur in patients who also have hepatitis B. This is because the hepatitis D virus needs certain hepatitis B viral proteins in order to replicate. The virus cannot reproduce without these structures.

It is possible to become infected with hepatitis D virus and hepatitis B virus simultaneously. Transmission of the virus is also possible in patients who already have chronic hepatitis B. Infection with the hepatitis D virus may cause a more severe inflammation of the liver than chronic infection with hepatitis B virus alone.

Hepatitis D occurs in particular in southern countries (Mediterranean countries, South America, Africa). If you have chronic hepatitis B, you should ask your doctor how best to protect yourself against hepatitis D. You should always try to avoid traveling to countries with a high prevalence of hepatitis D virus infection.

Blood tests

Hepatitis B is diagnosed by testing for various antigens and antibodies (see table page 7). The main markers are anti-HBc antibody and HBs antigen. If an HBs-Ag test is positive, further tests should be done to establish the hepatitis activity. These tests are HBe-Ag and anti-HBe assays and direct measurement of the amount of virus DNA in the blood (viral load).

Liver function tests (ALT, AST) are of limited value in indicating the inflammatory activity associated with hepatitis. The disease activity and connective tissue reaction in the liver can be evaluated reliably only by investigating a sample of liver tissue. Non-invasive procedures such as elastography give an indirect indication of the degree of fibrosis.

Since patients with chronic hepatitis B are at greater risk of developing liver cancer, alpha-fetoprotein (AFP), a tumor marker for liver cancer, should be monitored and ultrasound scans of the liver should be done at half-yearly intervals.

Liver biopsy (liver tissue sampling)

In order to estimate the extent of connective tissue infiltration and inflammatory activity in the liver, for example as a basis for deciding on treatment, liver biopsy is recommended. Biopsy of the liver involves the removal of a small piece of tissue (with the patient under local anesthesia) for histological examination under a microscope. Another liver biopsy after completion of treatment may be indicated in order to assess the response to treatment. Non-invasive procedures (lab markers, elastography) are fairly reliable predictors of cirrhosis even in the absence of liver biopsy.

Treatment of chronic hepatitis B

Treatment with virostatics

In recent years, a large number of agents (virostatics) have been tested for their ability to directly inhibit virus replication. Treatment of chronic hepatitis B does not usually eliminate the virus from the body. In some patients, a high-replicative form of the disease (high viral load) can be converted to a low-replicative form (low viral load) on a permanent basis. The bulk of patients require long-term, in some cases life-long treatment to stop the disease from

progressing. That is why it is so important to discuss the necessity of treatment and goals of treatment in detail with the doctor. As a rule, treatment is always necessary if there is major inflammation of the liver and high enzyme levels in liver function tests, major connective tissue reactions in the liver, and if there is a high concentration of HBV-DNA (viral load) in the blood. Lamivudine, adefovir, entecavir and telbivudine can help to inhibit viral replication and chronic hepatitis B activity. These drugs are known as nucleoside or nucleotide analogues.

When is treatment with nucleoside/nucleotide analogues carried out?

Basically anybody with chronic hepatitis B may be treated with lamivudine, adefovir, entecavir or telbivudine. Responses to these drugs have also been reported for patients who had little chance of a sustained response to interferon treatment. Patients who did not respond to interferon-alfa treatment in the past and patients who are unable to receive interferon-alfa because of another underlying disease (e.g., immunodeficiency, post-transplant situation, HIV infection, etc.) may also be treated with nucleoside/nucleotide analogues. Lamivudine, adefovir, entecavir and telbivudine are taken in tablet form. The dose levels are as follows:

Lamivudine: 100 mg daily

Adefovir: 10 mg daily

Entecavir: 0.5-1.0 mg daily

Telbivudine: 600 mg daily

Side effects of nucleoside/nucleotide analogues

Unlike interferon, lamivudine, adefovir, entecavir and telbivudine are very rarely associated with side effects. There are reports of headache, fever, rash, general malaise, gastrointestinal symptoms, insomnia, cough and several case reports of pancreatitis. Kidney function should be monitored regularly in patients on adefovir.

Resistance to lamivudine tends to be more common and more rapid compared with other agents. The incidence of resistance is 30% for lamivudine, 15% for telbivudine, and less than 2% for adefovir and entecavir at two years. Five-year resistance rates are 70% for lamivudine and 28% for adefovir. Fortunately, hepatitis B viruses that have become resistant to lamivudine and telbivudine respond to adefovir and vice versa, i.e. viruses resistant to adefovir respond to lamivudine and telbivudine. Therefore, it is essential that two appropriate drugs are taken together (combination therapy) once resistances develop. It is also becoming common practice for patients with an unsatisfactory virologic response to receive a suitable second drug at an early stage, in order to prevent resistances from developing in the first place.

Treatment with (pegylated) interferon-alfa

Interferon-alfa is a protein produced naturally by the body, e.g. by the white blood cells. Interferon is produced in particular when the body has to mount a defense against disease-causing organisms. The interferon used to treat chronic hepatitis – **Interferon-alfa** – is produced by biotechnology. Like, for instance, the insulin used to treat patients with diabetes, interferon-alfa is injected into the fatty tissue layer below the skin. More recent interferons (called pegylated interferons) have a longer duration of action and only need to be injected once per week.

How is treatment carried out?

Formerly, chronic hepatitis B was treated with three weekly doses of 5–6 million international units (IU) of standard interferon-alfa. More recent studies used long-acting pegylated interferons at a dose of 180 µg/week (peginterferon alfa-2a) or 50–100 µg/week (peginterferon alfa-2b). Treatment with peginterferon-alfa should be continued for 48 weeks. 30%–35% of patients respond to peginterferon-alfa for the treatment of chronic hepatitis B. These figures apply to patients with detectable levels of the HBe antigen. The sustained response rate for other patients, e.g. those infected with a variant of the hepatitis B virus (called HBeAg minus mutants), is 20%. The aim of treatment is to inhibit virus replication, i.e., to convert high-replicative chronic hepatitis B to low-replicative chronic hepatitis B. Hence, hepatitis B treatment helps to control the virus rather than eliminate it comple-

tely (eradication). In ideal cases (up to 3%), treatment with peginterferon removes all traces of the HBs antigen, which equates with a cure.

Side effects of pegylated interferon-alfa

Side effects are common at the start of interferon-alfa treatment and usually become much less severe as treatment progresses. The most common side effects are flu-like symptoms such as fever, headaches, pains in the joints and muscles, fatigue, lack of appetite and weight loss. Thyroid dysfunction occasionally occurs. Some patients temporarily lose their hair during treatment. Mood changes to the point of depression may also occur. Other major side effects are changes in the composition of the blood, especially with regard to the white blood cell count. Pegylated interferons have the same spectrum of side effects as standard interferons.

Combination treatments

The results of the first studies on treatment regimens combining pegylated interferons and nucleoside/nucleotide analogues (e.g. lamivudine) were disappointing, as these regimens did not improve the sustained virologic response rate.

Combining two virostatics (e.g. lamivudine plus adefovir) is not more antivirally effective than using one on its own. However, it may be useful in preventing resistance from developing in at-risk patients (e.g. before and after a liver transplant). In patients who have developed resistances, combination treatment is essential.

Vaccination against hepatitis B

A vaccine against hepatitis B is available. It has been recommended for infants, small children and youngsters. Other populations who should undergo hepatitis B vaccination include people with a high risk of exposure through their work (medical and dental professions, the police force, first-aid workers), dialysis patients, all patients with other chronic liver diseases (e.g. chronic hepatitis C), people living in close contact with people with chronic hepatitis B, and babies born to infected mothers.

Three injections of the vaccine are required to ensure adequate protection, after which 90 % of those vaccinated are safe from infection.

Nutrition and hepatitis B

People infected with chronic hepatitis B do not require a special diet as long as their liver function is not impaired. People with impairment of their liver function may need to limit their protein (meat and dairy products) and salt intake. Your doctor should discuss this with you, with the support of a dietician as appropriate. It is important for you to avoid alcohol.

About ELPA

ELPA emerged from a desire amongst European liver patient groups to share their experiences of the often very different approaches adopted in different countries. In June 2004, 13 patient groups from 10 European and Mediterranean Basin countries met to create the association. ELPA was formally launched in Paris on April 14th 2005 during the annual conference of the European Association for the Study of the Liver (EASL) and now has 20 members from 14 countries.

ELPA's aim is to promote the interests of people with liver disease and in particular:

- to highlight the size of the problem;
- to promote awareness and prevention;
- to address the low profile of liver disease as compared to other areas of medicine such as heart disease;
- to share experience of successful initiatives;
- to work with professional bodies such as EASL and with the EU to ensure that treatment and care are harmonised across Europe to the highest standards.

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