



Comprehensive Guideline for

HEPATITIS C

People Awareness

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PREFACE

Chronic viral hepatitis B and C are common diseases across the world and can be controlled through increasing public awareness and informing individuals about their routes of transmission and their methods of prevention and treatment. Hepatitis C, in particular, is one of the cause of hepatic insufficiency (liver failure) and cirrhosis. In recent years, the treatment of hepatitis C has undergone extensive developments and a hepatitis C free society is predicted to arise in the future with the use of new medications. The number of cases with hepatitis can be reduced and new cases of infection can be prevented through identifying and treating infected people and taking note of the risk factors associated with the disease. Increasing public awareness and knowledge is one of the main factors for controlling hepatitis C. I hope for world without hepatitis C in future, the desire is difficult but not impossible!.

**Seyed Moayed Alavian MD,
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A Comprehensive Guide For Hepatitis C

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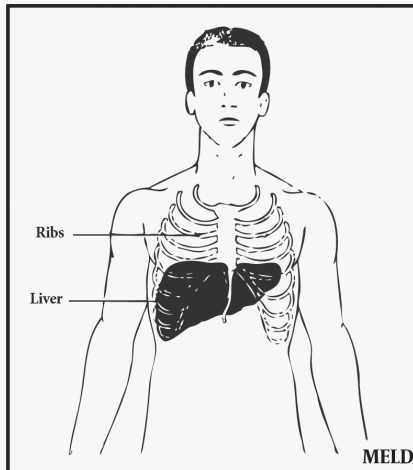
Structure and function of the gastrointestinal tract

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.

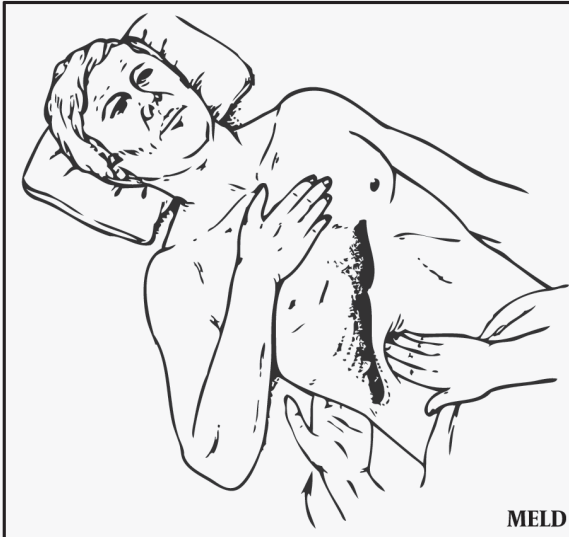
Structure and function of the gastrointestinal tract

► 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.



Structure and function of the gastrointestinal tract

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



► Liver's functions:

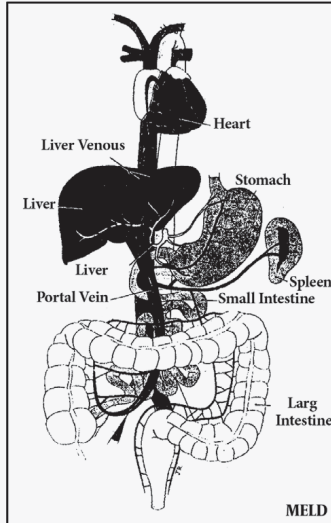
Liver is one of the largest internal organs and performs various vital functions in human body, the most important of which are mentioned below:

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:



Structure and function of the gastrointestinal tract

- 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 function-

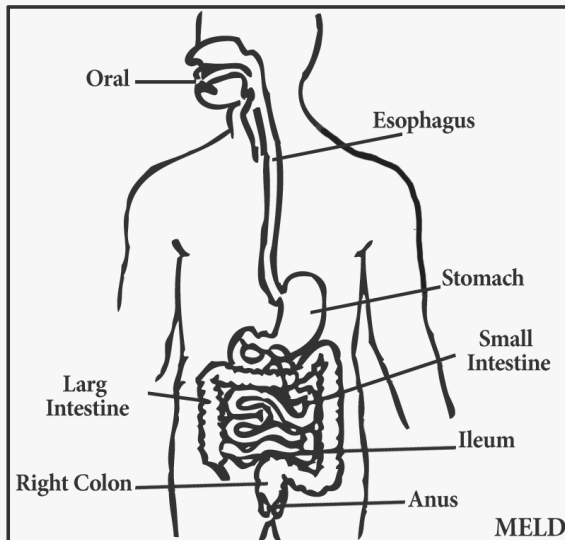


► Protein production

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-

Structure and function of the gastrointestinal tract

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.



A Comprehensive Guide For Hepatitis C

CHAPTER 02

What are hepatitis and its different types?

Hepatitis refers to the inflammation of the liver and is also called jaundice. Viruses are the main cause of hepatitis, which is considered acute when the disease and its symptoms last under 6 months and chronic when they last over 6 months. Hepatitis is a major healthcare problem across the world today and the different types of hepatitis vary considerably in terms of their prevalence, causes, and routes of transmission depending on the level of hygiene, traditions, social habits and the degree of abiding by moral codes of conduct. Human beings have long been familiar with hepatitis; the Greek philosopher, Hippocrates, also wrote on this disease. During the American Civil War and the First World War, hepatitis was a great danger that knocked out many soldiers from the battle field and inflicted irreversible damages on the army. As recorded in medical reports, during the Second World War, too, a large number of people in the Middle East and Italy were infected with hepatitis due to poor sanitation and hygiene conditions.

What is hepatitis?

► What are the causes of hepatitis?

Throughout the years, countless people have gotten infected with hepatitis and many have died from the disease. Approximately 70,000 soldiers were infected with (viral) hepatitis during the First World War, and physicians found that there were two types of hepatitis in the Second World War. The first type is infectious and orally transmitted (mainly hepatitis A), and the second type is serum hepatitis transmitted through the blood (such as hepatitis B).

Different factors cause the inflammation of the liver. Viruses are the most common causes of hepatitis. Viruses are microorganisms that cannot be seen with the naked eye and require advanced equipment such as electron microscopes to be seen. Viruses are composed of a set of genetic materials and proteins. Viruses cannot survive outside the body but proliferate quickly within hours inside the body. At least 6 types of viruses have been identified to cause different types of hepatitis, which were then named based on the English alphabet, including hepatitis A, B, C, D, E and G viruses. Each virus belongs to a distinct group and the diseases they cause are not related. Hepatitis B virus was properly identified in 1960s and hepatitis A virus in 1973; however, hepatitis C virus remained a mystery for years until it was finally identified in 1989.



2.1: Overview of a hepatitis virus



Liver is the locus for the replication and growth of hepatitis viruses. The growth of viruses disturbs the liver functions.



► Symptoms of hepatitis

The majority of patients with viral hepatitis do not present any symptoms for the disease and their disease is accidentally diagnosed through routine tests. Some patients, however, present acute symptoms of the disease.

Following contact with a hepatitis virus and after the incubation or latency period of weeks or months, acute symptoms of hepatitis emerge.

Symptoms of hepatic diseases vary from one case to another. Symptoms of hepatitis also range from a state of cold and flu, anorexia, lethargy, malaise, dark urine, pale stools, itching and headache to a severe jaundice, which is called acute hepatitis.

What is hepatitis?

These symptoms are not specific to any one type of hepatitis and are rather seen in all types of the disease. In 95% of the cases with acute hepatitis, symptoms automatically disappear (even without treatment) within 4-6 weeks and the virus is excreted from the body. In 5% of the cases with hepatitis B, the causing virus remains in the body and makes the patient a carrier.

Symptoms of acute hepatitis

- **Yellow discoloration of the skin and eyes (jaundice)**
- **Dark urine**
- **Pale stool (clay-colored stool)**
- **Nausea and vomiting**
- **Anorexia**
- **Itching**
- **Fatigue, lethargy and decreased ability to perform daily activities.**



Are hives a symptom of hepatitis?



In most cases, no.

In some cases, after the incidence of hepatitis, skin lesions such as hives emerge that are caused by the deposition of hepatitis antigens in the skin. Chronic hives are not, however, a symptom of hepatitis in most cases.

Hives are considered a disturbing complication that is periodically experienced by some patients, and its etiology is unknown in most cases despite the different tests performed. Iranians are inclined to incorrectly associate most of their skin problems with the liver.

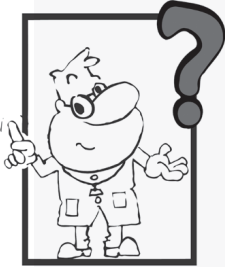
Hives are caused by many different factors, including food and drug allergies, chronic infections such as sinusitis, tooth infections, gallbladder diseases and parasitic infections.



► What is jaundice?

Jaundice refers to the yellowing of the skin and white of the eyes due to high levels of blood bilirubin. Bilirubin is produced regularly on a daily basis after the breakdown of red blood cells and is excreted from the body by the liver through the bile. In the case of liver dysfunction (such as hepatitis) or biliary outflow obstruction (for example, the presence of gallstones), blood bilirubin is not excreted from the body and instead accumulates in the body and causes jaundice. The incidence of jaundice is not necessarily a symptom of hepatitis and might have other reasons. For instance, the excessive breakdown of red blood cells (hemolysis) may cause jaundice. Many patients with hepatitis and especially carriers of hepatitis B do not have a history of jaundice and are not yellow in color either. Symptoms of the disease should be interpreted by physicians only.



Does indulgence in carrots cause jaundice?

Yes;

this condition occurs mostly in children, but the resultant yellowing is different from jaundice. Most fruit and vegetables, including carrots and tangerines, contain a yellow pigment known as carotene. If someone drinks a glass of carrot juice every day (or indulges in the other nutrients mentioned), carotene level increases in their body to the extent that their liver cannot metabolize and excrete it anymore and its blood level therefore increases. The pigment eventually accumulates under the skin and turns it yellow. The main difference between this type of yellowing and the yellowing caused by hepatic or blood diseases is that the white of the eye (the sclera) does not turn yellow in the yellowing caused by the accumulation of carotene pigments in the blood (following indulgence in a particular nutrient). In these instances, if consumption of the particular nutrient is reduced, the yellowing gradually diminishes within weeks and does not cause problems. The incidence of jaundice is not necessarily a symptom of hepatitis and might have other reasons.



What is hepatitis?

► Does the incidence of hepatitis necessarily imply death?

No. The course of the disease varies with the severity and type of hepatitis. Hepatitis A has a very low rate of mortality and does not leave any complications after recovery, either. Hepatitis B is cured in most cases; however, in 5% of the patients, the virus remains in the body and leads to potential problems in the future through proliferation. Hepatitis C disappear in 30% of patients spontaneously and in remind of patients it progress slowly during 20-30 years.





A Comprehensive Guide For Hepatitis C

CHAPTER 03

Hepatitis C

After the identification of hepatitis A and B viruses in the 1970s, researchers started looking for the causes of different types of viral hepatitis that were not caused by the known A and B viruses and it took them years to finally achieve presentable results. In 1989, Michel Houghton et al. made great developments in the science of hepatic diseases with the use of new molecular biology techniques and through isolating the hepatitis C virus for the first time. The infection is transmitted through contact with infected blood. Given that the virus is not easily eliminated by the host immune system, infection with the hepatitis C virus often results in a persistent infection in the body. Some researchers attribute the origin of hepatitis C virus to Asia; many people were infected with the disease during the world war. The species of this virus found in Thailand revealed it to have been present in Asia for a long time and to have been in a state of transformation. Men who were infected with hepatitis C in the Far East during the wartime due to blood transfusions, injuries, etc., spread the disease through various ways, including blood donation, after their return home. Among the hepatitis viruses identified to date, hepatitis B and C viruses are known as the major causes of lazy liver, a chronic hepatic disease, and controlling them is a priority.

What is hepatitis C?

Infection with one type of hepatitis virus does not safeguard the patient against other types of viral hepatitis.

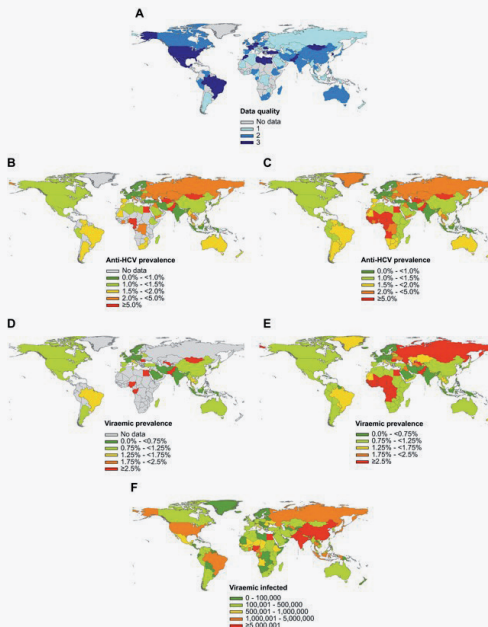


► Cause of hepatitis C

Hepatitis C virus belongs to the genus *Flavivirus*. Hepatitis C virus is an enveloped single-stranded virus 50-60 nm in size. It proliferates in the liver cells and damages them. Hepatitis C is a virus transmitted through the blood. Hepatitis C virus was identified in 1989 and a blood test for checking hepatitis antibodies was introduced in 1990. Researchers believe that hepatitis C virus has various species and can cross the barrier of the host immune system and cause chronic infections due to its genetic diversity. According to genetic studies, the virus has 7 species and some subspecies. The significant geographic diversity in the prevalence of species and subspecies is due to the high mutation rates of the virus. Re-infection with hepatitis C is also possible since no persistent immunity is developed against it. A map of the various genotypes (species) of the virus can be currently perceived based on the geographical distribution of the disease in the Middle East

and Central Asia. The virus genotype might be helpful in the prediction of the disease's responsiveness to treatments, its methods of treatment and even the duration of treatment and type of medications.

The most prevalent genotypes in Iran are 1a, 3a and 1b, in respective order of prevalence. Genotype 4 is more prevalent in Arab countries of the region, including Syria, Egypt, Iraq, Kuwait and Saudi Arabia, while genotype 3a is more prevalent in Pakistan and genotype 1b in Azerbaijan, Tajikistan, Russia and Turkey.



What is hepatitis C?

► Transmission routes of hepatitis C

Infection with hepatic C virus is a major health problem across the world today and is considered a challenge that will certainly turn into a disaster in the future if necessary measures are not taken to control and prevent it today. It is estimated that about 200 million people are infected with hepatitis C in the world today. The disease is more prevalent in East Asian countries, Egypt, Pakistan and Azerbaijan; however, the exact number of infected people by country is not available.

Hepatitis C virus is transmitted through contact with an infected person's blood. The virus survives outside the human body and in dried blood for up to three months but is killed if boiled at 100°C for 5 minutes.



The most common transmission route for hepatitis C virus in the world until 1992 and in Iran until 1995-6 was the receiving of infected blood and blood products. After this date, however, all blood supplies were tested for all the different types of infectious diseases, including hepatitis C, and were allowed to be injected only if clean. The failure to test blood supplies for hepatitis C before this date was due to the impossibility of performing hepatitis C testing –in other words, that the virus was unknown. Repeated recipients of blood products, including coagulation factors VIII and IX for patients with hemophilia and blood in patients under hemodialysis for chronic kidney failure, are at a serious risk of contracting hepatitis C. Intravenous drug addiction and contact with infected people’s blood as a result of sharing needles are important risk factors for contracting hepatitis C. Over 75% of people currently addicted to intravenous drugs or with a history of the addiction have contracted hepatitis C. It should be noted that the cause of the disease cannot be determined in 30-40% of the cases, making for an unknown transmission.

- Patients with hepatitis C are generally divided into 4 general groups:

1- First group: People who are at risk due to their history of receiving blood and its products, such as patients with hemophilia and thalassemia or patients on dialysis;

2- Second group: People with a history of blood injection prior to 1992 when blood supplies were not tested for hepatitis C;

What is hepatitis C?

- 3- Third group:** People who are addicted to intravenous drugs or have multiple sex partners;
- 4- Fourth group:** 30-40% of the total number of patients with unknown cause of infection

The widely-held opinion is that there are other transmission routes for this disease that may have not been detected as of yet. Some routes of transmission will be discussed at length here.

Patients afflicted with the disease are encouraged not to be distraught with some of the transmission routes mentioned here as they are not particular to each and every patient. Physicians are responsible for identifying and examining transmission routes.



► **Hepatitis C and blood injection**

Hepatitis C virus is a blood-borne virus and blood injection was the main route of transmission for the disease before the introduction of tests for detecting the virus (HCV Ab). This disease is more prevalent in people who regularly receive blood and its products, such as patients with hemophilia and thalassemia or patients on dialysis. This trend shows the greater significance of infected blood and blood products in the transmission of the disease. In the course of its progress, medical science has taken a step toward screening the blood used for injection. For instance, the prevalence of hepatitis caused by the injection of blood decreased considerably after the introduction of the HBs Ag test (for the diagnosis of hepatitis B) in 1970 and the screening of all donated blood for hepatitis B and the removal of infected blood. Another example is provided for further clarification. The HIV was discovered in the 1980s and finding disease detection methods used for screening donated blood made up for another advancement in this area. The risk of the transmission of hepatitis and infectious agents through blood transfusion was further reduced after the identification of hepatitis C virus in 1990 and the use of HCV Ab tests for the detection of blood infected with the virus and discarding the infected blood in 1992. Nevertheless, the main risk is posed by blood donors with hepatitis C virus present in their body whose virus antibodies (to be detected by a hepatitis C test) are not positive yet; blood transfusion from such individuals to others causes problems.

What is hepatitis C?

The safety of blood and its products becomes more reliable with the increased accuracy and sensitivity of diagnostic tests for hepatitis C virus.



? Is hepatitis C transmitted through the transfusion of blood and its products nowadays?

Before testing blood for hepatitis C became possible in 1992 in developed countries and in 1995-6 in Iran, the most prevalent route of transmission for the disease was the use of blood and its products, and hepatitis C was then responsible for 90% of hepatic diseases following blood transfusion. The various tests performed today have guaranteed the safety of blood. The risk of infection with hepatitis C after the injection of blood is very low nowadays, although it is not yet zero anywhere across the world.

The use of blood and its products is no problem at the physician's discretion if necessary. Patients should not worry about hepatitis C transmission nowadays.



▶ **Hepatitis and patients with special diseases**

As already noted, patients with hemophilia, thalassemia and chronic kidney failure on dialysis are prone to the risk of contracting hepatitis C. According to the available statistics, over 15% of patients with chronic kidney failure, 75% of hemophilia patients and 20% of patients with thalassemia are infected with hepatitis C. Each of these diseases will be discussed later in their own dedicated chapters.

▶ **Hepatitis and addiction**

Intravenous drug addiction is one of the major causes of infection with hepatitis C. The habit of sharing needles among addicts might lead to the transmission of all types of infections, including HVB, HVC and HIV. However, addiction to cocaine and sniffing through the nose make up for another route of transmission. A major risk threatening addicts is coinfection with different species of hepatitis C virus that cause a more severe disease. In such cases, the response to antiviral drugs is reduced.

? Some intravenous drug addicts do not express any history of sharing injection equipment with others. How is the infection with hepatitis C justified in this group?

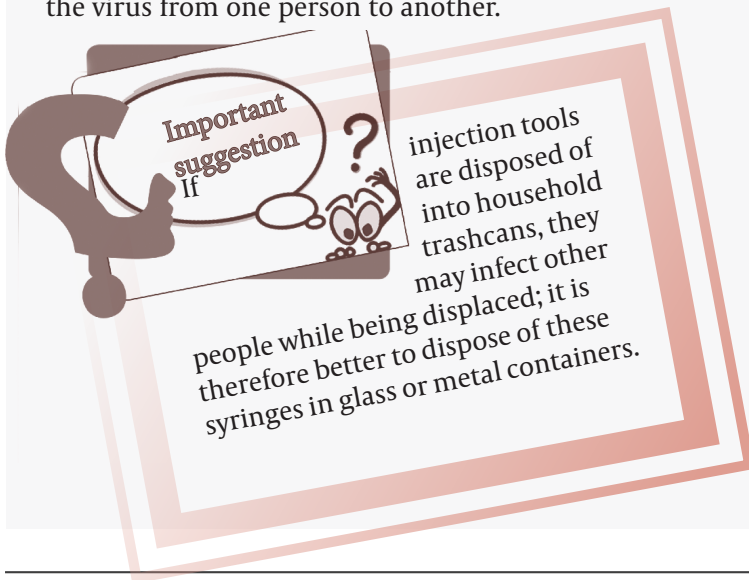
Sharing injection equipment even only once is enough for a

What is hepatitis C?

person to be infected with the virus. Many intravenous drug addicts do not express any history of sharing injection equipment, but the first experience of injection often takes place with the encouragement of friends and with the borrowing of their equipment. Sharing equipment even once results in the transmission of the disease. In many cases, the presence of the virus in the blood does not present any symptoms and even the infected patients are not aware of their infection.

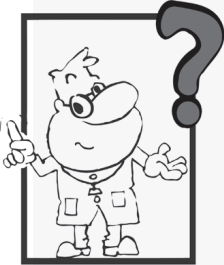
? **Does replacing the needle of shared syringes inhibit the transmission of the virus?**

No; all the equipment shared for injection contaminated with blood, such as the needle and the syringe, can transmit the virus from one person to another.



The prime way to prevent hepatitis C in addicts is withdrawal; otherwise, the alternative is to not to share injection equipment.

Are other forms of addiction involved in hepatitis infection?

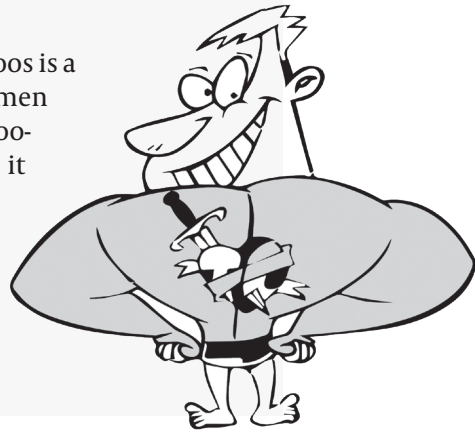


Yes;

other forms of addiction, such as sniffing (sniffing drugs through the nose) and smoking opium, are also effective, but are not as dangerous as intravenous drug addiction.

► **Hepatitis and tattooing**

Piercing the skin with a needle for tattoos is a known route for HCV transmission. Women should note that although eyebrow tattooing can make the face more beautiful, it might cost them infection with hepatitis. Nevertheless, if hygienic tattooing is practiced and only disposable equipment is used, there is no need to worry about infections.



One method of preventing hepatitis C is separating personal items, such as toothbrushes, razors, nail clippers, towels and bath equipment.

Contact between mucous membranes (e.g., the surface of the eyes) and blood or other secretions infected with blood such as saliva is one route of transmission for the disease, although it presents a rather low risk. Skin cuts and injuries should be carefully dressed with adhesive bandages.

There are no restrictions against the marriage of people with hepatitis C. Instead of worrying about transmitting the disease to other people, care should be taken to practice the codes of hygiene.

► Hepatitis and transmission to family members

The transmission of hepatitis C through sexual intercourse within a marriage is not common. Available statistics show a risk of less than 5% for infection in these arrangements. The level of transmission depends on the duration of the marriage and the amount of virus present in the blood of the infected partner. However, the risk of sexual transmission increases through sexual intercourse with multiple partners and outside marriage. The risk of transmission through sexual intercourse even within marriage can make families worried and affect their lifestyle, relationships and sexual relations. This

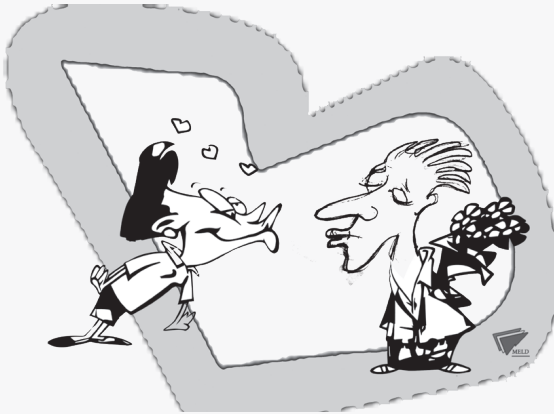


issue should be properly clarified for them. The risk of transmission through sexual intercourse within marriage is very low and certain guidelines for hygiene should be respected. Healthy sexual practices (I hope readers understand what I mean) performed when the wife is physically ready should not trigger concerns for infection. The risk of transmission to other family members is very low. It should be noted that having separate utensils and plates is not necessary; however, personal items such as toothbrushes, razors, nail clippers, combs, towels and washcloths should be separate. There is no evidence of the oral transmission of the virus, such as through infected food or water (unlike hepatitis A). Patients should not be over-sensitive to the risk of transmitting the disease to others and should not seek to isolate themselves, feel guilty and frequently blame themselves. The best approach is to gather a precise understanding of the disease and its routes of transmission and to always seek to practice codes of hygiene and to avoid superstitions. Prevent the transmission of infections, including hepatitis C, through separating your personal items.



► Hepatitis and sexual transmission

Marriage is one of the major events in any person's lifetime. Marriage of one's children is one of the dearest wishes of parents. After coming into maturity, young adults decide to get married taking both their own and the other party's conditions into account. There are no restrictions against marriage for patients with hepatitis C. Hepatitis C virus is present in the semen, vaginal secretions and saliva to a very low degree and there is a risk, albeit low, of infection after a sexual encounter with a patient who has hepatitis C. This risk is directly correlated with the duration of the marriage. Patients should pay attention to their sexual practices. Sexual relations within the family (i.e. with only one partner) and in compliance with codes of morality and hygiene are associated with a very low risk of infection. In western countries, this risk is increased due to the trend of having multiple sex partners and the performance of unusual sexual practices, such



as sexual relations during menstruation or anal/oral sex. There are no restrictions against marriage for patients with hepatitis C. Sexual relations with high-risk partners are associated with the risk of infection with hepatitis or HIV; however, sexual relations within the family are not problematic. Some researchers recommend the use of condoms during sexual relations within the family in order to prevent hepatitis C while some others do not find it necessary. When the family does not intend to conceive, it is recommended for the male partner to use condoms. There are no restrictions against normal romantic engagements with patients with hepatitis C, such as kissing.

.....
The presence of HCV in the semen and vaginal secretions does not signify the 100% chance of transmission of the virus. The risk of hepatitis C transmission is not high in safe sex.
.....



My husband is infected with hepatitis C, can I kiss him?

Yes; romantic engagements are vital in a marriage and there are no restrictions against them in this case, either.

What is hepatitis C?

? **I am a man of 27 diagnosed with HCV infection 2 years ago. I have proposed to several girls so far, but they have all turned me down with their families upon learning of my conditions. What am I to do?**

Your future wife has an absolute right to know of your conditions. If you were in the shoes of your intended wife yourself, you would expect to be informed of the disease before marriage. However, the manner of informing about such conditions is fundamental. You can ask for the help of an advisor or a specialist in the field. I always assert that **a husband with hepatitis C is better than a bad-tempered husband!**

► **Hepatitis C and its transmission from mother to infant**

The risk of HCV transmission from a pregnant woman to her embryo is very low. The risk of transmission to infants at birth is lower than 5% (1-3%). There is a risk of infection at birth because of the intermingling of maternal and fetal blood. The type of delivery (caesarean section or natural childbirth) does not contribute to the infection. Hepatitis C virus is rarely transmitted from a mother to her embryo.





Can the higher risk of transmission from infected mothers to infants be determined through a specific test?

Yes, if HCV RNA PCR test result is positive in mother’s blood and the viral titer is high, the risk of transmission to infants is increased.

.....
A slightly higher risk of HCV transmission from infected mothers to infants cannot deprive them of having children and breastfeeding.
.....



When after birth should the infants of infected mothers undergo hepatitis C testing?

The result of HCV Ab testing might be positive in infants after birth; however, it is not enough evidence for infection. The test is usually performed six months after birth.

.....
A study conducted on 120 infants of mothers with hepatitis C in Hamburg, Germany, showed that only 6 infants (5%) were infected with the disease.
.....

? **Can mothers with hepatitis C breastfeed their infants?**

There are no restrictions against breastfeeding. It should be noted, however, that there is a risk of transmission when the mother's breast is wounded or injured.

Human beings are the only source of hepatitis C virus and no animal sources have been found for it as of yet.

► **Hepatitis C and medical personnel**

The risk and prevalence of hepatitis C is higher in hospital personnel, physicians, dentists, oral and dental surgeons, nurses, paramedics, midwives and hairdressers. In general, anyone in close contact with the patients' blood is at the risk of infection with this disease, including hemodialysis centers' personnel and caregivers of patients with hemophilia and thalassemia, as well.

It is necessary for all these individuals to respect the codes of hygiene and to avoid



contact with blood because the incidence of the disease cannot be prevented by immunoglobulin after a contaminated needle stick accident.

.....

The general belief is that the tools used for ear piercing, acupuncture and dentistry may be infected with HCV and infect healthy people.

In 30-40% of the cases, no specific known routes of transmission can be found for infection with HCV.

.....

► **HCV is not transmitted through the following routes:**

- 1- Shaking hands with or kissing an infected person;
- 2- Cooking and eating in the same place as them;
- 3- Normal socialization in the workplace or at home;
- 4- Hugging the infected;
- 5- The air;
- 6- Swimming in the same pool.

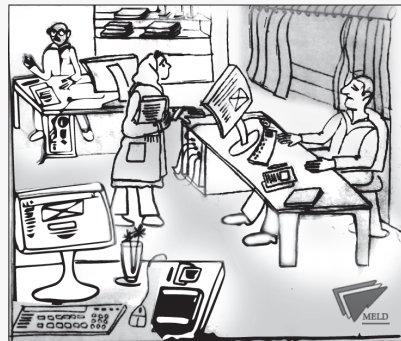
What is hepatitis C?

? I am working in a state department. One of my colleagues has hepatitis C. Can the disease be transmitted to us?

No; the usual forms of daily contact such as shaking hands, working in the same room and socializing with friends and classmates do not contain the risk of transmitting the disease and are not matter for concern. One should only make sure to respect all codes of hygiene.

? About 2 months ago, I hosted one of my friends. Some days ago, after I met him again, I found out he was infected with hepatitis C. Do you recommend that I go to a laboratory for hepatitis C testing?

No, that is not necessary. You should only avoid sharing razors and personal care products such as nail clippers with others even among circles of friends.





One of my friends is infected with hepatitis C. Can I go to his place for partying and eating?

There are no restrictions against hanging out with them. Even if the infected person is the one who cooks, you can be confident about hanging out with them and eating their food.

In general, the following people are at a higher risk for infection with hepatitis C and should undergo hepatitis C testing:

- 1- People with a history of blood transfusion prior to 1992 across the world and 1996 in Iran, since blood supplies were not tested for hepatitis C then;
- 2- Patients with hemophilia (a type of coagulopathy), chronic kidney failure (dialysis), and thalassemia who use blood and its products;
- 3- Medical personnel who are in contact with the patients' blood or who have had contaminated needle stick accidents;
- 4- People with unconventional or unsafe sexual behavior;
- 5- All intravenous drug addicts;
- 6- All wives or husbands of individuals infected with hepatitis C.



A Comprehensive Guide For Hepatitis C

CHAPTER 04

Diagnosing hepatitis C

Hepatitis C is diagnosed through anti-HCV antibody tests using the ELISA method. If the test result is positive, the more precise RIBA test (or Western blot analysis) should then be performed to prove the infection. Now PCR testing can be performed to prove the absence or presence of the virus. The person should not be considered infected until the result proves it. What makes the result significant is the person's general health status, medical records, liver status based on the tests, liver ultrasound and some other tests for examining viral activity in the body. It should be noted that hepatitis C virus destroys the liver cells rather mysteriously. The disease gradually progresses toward a chronic state; it fluctuates and the blood levels of the virus and the disease activity change transiently. The majority of patients with hepatitis C do not present any symptoms and a few experience fatigue and have a mild fever, abdominal pain or discoloration of urine, and these signs are variable, as well.



After a hepatitis C diagnosis, there are certain questions that need to be answered: Does the patient have a liver lesion? How severe is the liver lesion? Does the liver lesion need to be treated? And how should the patient protect his liver from more damage?

? **The majority of patients diagnosed with hepatitis express their disbelief in actually having hepatitis. What can be said of this issue?**

In general, when a patient is informed of his viral hepatitis (for example, hepatitis C), he will feel dejected and wonder why he has been infected with hepatitis C and what will become of him. It is recommended to always consult with a specialist of the field when first learning of the diagnosis.



In the majority of cases, the disease progresses slowly, and only 20-30% of the patients develop cirrhosis (or a lazy liver), which lasts 20-30 years. Potent treatments are currently available for these patients and new medications are being discovered by the day. In such conditions, physicians examine other

causes of the viral hepatitis, including hepatitis B virus and liver conditions (for example, a fatty liver). There are tests for examining liver functioning, including tests for examining liver enzymes (AST & ALT), bilirubin, albumin and the blood count.

▶ **What are liver enzymes?**

In general, liver enzyme measurements can provide a useful marker for determining the presence of the disease in the organ. AST and ALT are the main liver enzymes. The increase in serum levels of these enzymes shows the inflammation of the liver.

? If liver test results, such as ALT and AST (aminotransferases) levels, are normal, can we be sure the patient with hepatitis C has no liver lesions?

No; in a few patients, hepatic histology shows lesions despite the normal status of biochemical enzymes (such as aminotransferases).

? Is PCR or HCV RNA testing recommended for all patients with hepatitis C?

Yes; hepatic blood test (AST & ALT) results may be normal in patients with hepatitis C; PCR testing should therefore be necessarily performed for all patients to examine the viral activity.

► What is chronic hepatitis?

Chronic hepatitis refers to the condition in which hepatitis C virus is present in the body for more than 6 months and liver damage is diagnosed following an increase in liver enzymes and positive PCR test results. In such conditions, liver damage worsens and a lazy liver might be the long-term outcome. Numerous studies have been conducted aiming to understand the course of hepatitis C.

Contrary to expectations, symptoms of the disease progress slowly and patients do not face any problems in the short term. Some studies did not find any particular disabilities in patients even up to 20 years after the infection (note: after infection, not after the diagnosis, which are two different things). Personal factors, such as age at the time of infection, sex (male or female), route of infection and alcohol consumption, are important in determining the age of the disease. The virus type (genotype) is also an important determinant of the disease's severity. The immune system cannot eliminate the virus within 6 months in 85% of patients, whose disease therefore becomes chronic. The virus is permanently present in these patients' blood and only its amount is subject to periodical changes. Chronic hepatitis is an insidious disease that progresses at a very low rate in most patients without presenting any physical symptoms. During the two decades performing liver biopsy, the status of the inflammation and the severity of the lesion are determined and scored according to the Nodal formula with a maximum score of 22.

► What is liver biopsy?

The first liver biopsy was performed in 1883 by Paul Ehrlich and then widely used during the Second World War in order to study viral hepatitis, which had infected a significant portion the war force. Liver biopsy is a diagnostic procedure for examining liver lesions and for determining their level of deterioration. The biopsy specimen collected is a few millimeters to a few centimeters in size and gets examined at a pathology laboratory. The accuracy and expertise of the laboratory is crucial to the diagnosis of the lesion.



How long does performing the liver biopsy take? And how should I prepare for it?

Preparing patients for liver biopsy takes 10 minutes, but the biopsy itself takes only 5 seconds. Patients should normally be fasting for 6 hours before their liver biopsy and rest for up to 6 hours after the procedure under the supervision of experienced nurses and while still fasting. Liver biopsy is

performed using a special needle called a Menghini needle or an automatic or semi-automatic disposable needle. It is necessary to also take a liver ultrasound and perform coagulation tests, such as platelet and hemoglobin prothrombin time (PT).

If you use antihypertensive drugs and/or blood thinners such as aspirin, make sure to inform your physician before the biopsy.

► The liver biopsy procedure

The skin at the site of biopsy is first disinfected with Beta-dine. Patients are advised not to touch the site and to cooperate with the medical personnel during the biopsy procedure. The physician asks the patient to hold his breath for a few minutes so that the biopsy can be performed within seconds. During liver biopsy, only a small part of the liver is removed, and the liver tissue is fully repaired within a few days and no liver damage is caused by the procedure.



? What are the risks of liver biopsy?

Liver biopsy is completely harmless and has bleeding as its main complication, which, however, occurs very rarely. Abdominal pain is another complication of liver biopsy that is only seen in a few patients and resolved with pain killers.

? Which specialist performs a liver biopsy?

Liver biopsy is often performed by a gastroenterologist, hepatologist or radiologist, but other specialists can also perform it. Selecting a physician who performs lots of biopsies presents a lower risk of complications. Today, liver biopsy is guided by an ultrasound and is therefore almost harmless.



The following instructions should be observed after a liver biopsy:

1-Patients should not leave the bed for 6 hours after the biopsy (even for using the bathroom) and are recommended to lie down according to the physician's instructions.

2-Nurses should consistently control the patients' blood pressure

Diagnosis of hepatitis C

and pulse. This is a routine procedure that should not worry the patients.

3- Patients should avoid eating and drinking for 6 hours after the biopsy and then start with drinking liquids and then eating solid food if bearable and if no vomiting occurs.

4- Patients should have a companion when being discharged from the hospital and should avoid driving.

5- Patients should avoid lifting heavy loads and having sexual intercourse for 3 days after the biopsy.

6- Patients can resume their daily activities and work after 24 hours and are also fit for traveling again by then.

7- Patients can remove the dressing on the site of their liver biopsy and take a shower after 24 hours. Often, the dressing does not need to be replaced.

If you experience abdominal pain, frequent vomiting or black stools after you have been discharged from the hospital, please contact your physician.



► **Fibroscan, a modern method of diagnosis**

Liver stiffness can be measured using the novel technology of sending low-frequency ultrasound waves into the body. The degree of liver stiffness is directly correlated with the degree of fibrosis and persistent liver damage. This non-invasive method can even be performed in pregnant women. The degree of liver fibrosis is scored within a range from F0 to F4 and the degree of liver stiffness is also measured and reported in kilopascals (kPa).

The results are analyzed in a complicated software and the degree of persistent liver damage (fibrosis) is determined through measuring the speed of waves using statistical formulas. This method is completely pain-free. Inaccuracy of liver biopsy is one per fifty thousand livers while the inaccuracy of fibroscan is one per five hundred thousand livers, which shows the higher accuracy of fibroscan for the measurement of liver damage.



MELD



A Comprehensive Guide For Hepatitis C

CHAPTER 05

Prevention

Infection with hepatitis C has unpleasant consequences. Prevention is better than treatment given the latter's more difficulty and higher costs. Effective vaccines have not yet been developed for the prevention of hepatitis C; however, scientific centers across the world are working on finding one. Studying the disease's routes of transmission and preventing from its expansion is crucial.

► Necessary care practices for preventing the infection of others:

- 1- Not sharing nail clippers, razors and tooth brushes.
- 2- Thorough disinfection of blood-contaminated areas.
- 3- Covering skin cuts and wounds with adhesive bandage in patients.
- 4- Careful disposing of syringes used for the injection of medications such as interferon in order to avoid wounding others.
- 5- Use of condoms during sexual activities.



When visiting the dentist's office, note that the dentist is at a risk of infection due to his contact with your oral secretions and blood and that there is also a risk of transmission to others (if the codes of hygiene are not carefully respected for the tools used). Make sure to inform your dentist of your condition in advance. Some dentists might reject you, but lying is not a recommended alternative even in such cases.

The Blood Transfusion Organization strongly advises patients with hepatitis C to avoid donating their blood.





Answers to some questions

I am a 45-year old man and have donated my blood several times during 1989-90 , and the card issued for me after the blood transfusion indicated my health every time. However, I received a letter from the Blood Transfusion Organization after a recent blood donation. The letter claimed that I have a partial blood disorder. I then went to a laboratory that confirmed my infection with hepatitis C. Why wasn't this condition detected during my previous blood transfusions? Does blood donation infect the donors with this disease?

Before 1992, donated blood was tested only for hepatitis B and HIV, and infection with hepatitis C virus could not be tested prior to this date. It is 25 years now since the identification of hepatitis C virus in the world and tests for detecting the virus became available only in 1992. Possessing a health card issued prior to this date does not reject your infection with hepatitis C during that time period. There is still the chance that you might have contracted the disease after 1992 through contact with hepatitis C virus; and one route for the transmission of hepatitis C is poor hygienic conditions in dentistry.

Given that only disposable tools clean of infections are used

for drawing blood from the donors, there is no risk of infection with hepatitis C for blood donors. However, given your infection with hepatitis C, please refrain from donating blood and visit Middle East Liver Diseases Centers in Iran and other countries of the region

(www.meldcenter.com)

بیمارستان تخصصی و فوق تخصصی منطقه آزاد کیش
Kish Free Zone Specialty & Sub Specialty Hospital

M.E.L.D Center

فیبرو اسکن
FIBROSCAN

از سلامت کبد خود اطمینان حاصل کنید

مرکز بین المللی بیماری های کبد کیش
Kish Middle East Liver Diseases

انجام تست تشخیصی فیبرو اسکن
با بهره گیری از تجهیزات
پیشرفته و به روز

.....

Patients with hepatitis C may sometimes need to have their blood drawn out due to their increased blood viscosity (high hemoglobin levels). In these conditions, venesection is performed according to the physician's recommendations and the collected blood is instantly thrown out.

.....

► Hepatitis C and hepatitis B vaccines

To prevent hepatitis B, patients with hepatitis C should be vaccinated for hepatitis B three times with a one-month and then a six-month interval of the first vaccination. Hepatitis B vaccination protects against hepatitis B only and does not prevent infection with other hepatitis viruses.



How can we can kill the virus present in the clothes and personal items of patients with hepatitis C?

The simplest way to kill the virus is to boil the infected clothes and personal items after removing all traces of the blood. If boiling is not possible, 5% bleach solutions can be used. These items are first put to soak in the bleach for half an hour and then washed normally with tap water. Colored clothes are better be soaked in 70% alcohol and then washed normally with water. The bleach can be prepared of one part bleach

(for example, 1 lit) and 10 parts water (for example, 10 lit).

It must be noted that the above procedures should only be taken when clothes are contaminated with blood.

? Should patients with hepatitis C bring their own razor and blade or shaving machine to the hairdresser's in order to prevent the transmission of the disease to others?

Patients are recommended to bring their own tools to the hairdresser's. Regardless, hairdressers should replace their blades as well as respect the codes of hygiene when providing service to their customers.





A Comprehensive Guide For Hepatitis C

CHAPTER 06

To hemophilia patients

Hemophilia is a hereditary coagulation disorder. The disease has been known since several thousand years ago, but got its name hemophilia, meaning a lover of blood, in 1882, and its different types (hemophilia type A, B, etc.) were then gradually introduced. The patients' longevity has increased given the advances in medicine and the possibility of providing essential care services and the changes in the patients' lifestyle. In a not-so-distant past, death due to different bleeding conditions was an anticipated outcome of hemophilia for patients. In 1973, Birch reported the death of 82 patients out of the 113 hemophilia patients surveyed before the age of 15. The introduction of fresh plasma in the 1950s and 1960s made some recoveries in the conditions of hemophilia patients, who were then promised a more normal life with the introduction of concentrated coagulation factors in the 1960s. Hemophilia patients should use coagulation products in order to maintain their quality of life. The early plasma derivatives contained infectious agents such as hepatitis B and C viruses, HIV, cytomegalovirus, and spirochete. The increasing advances of medicine toward the discovery of the unknown and the elimination of the risks of using blood and its products helped protect hemophilia patients against the risk of infectious diseases to a great extent in addition to improving their quality of life.

▶ Viral hepatitis

To prevent hepatitis B, patients with hepThe last two decades have been witness to a mass identification of all varieties of viral hepatitis and their nature across the globe. Investigations show that 350 million people in the world carry the hepatitis B virus and 1-4% of the world population are infected with the hepatitis C virus. Considering that infection with these two types of viruses might become chronic, efforts should be directed toward their prevention.

▶ Hepatitis B

According to studies conducted in 1987-1988, the prevalence of hepatitis B among hemophilia patients in different health centers across the world is 3-13%. In the case of contact with hepatitis B virus, the body's immune system automatically eliminates the virus in most cases.

In general, the prevalence of liver diseases caused by hepatitis B is higher in hemophilia patients compared to the normal population. For more information, please see the comprehensive book of hepatitis B by the same author.

Given that the risk of the transmission of hepatitis through the use of blood and its products has not been reduced to zero in any part of the world, and also given the patients' frequent hospitalizations, oral and dental surgeries and frequent injections, taking preventive measures for avoiding infection with hepatitis B is crucial.

Hepatitis C vaccination is recommended for all hemophilia patients.

► Hepatitis C

All hemophilia patients who had used coagulation factors before 1985 were infected with hepatitis C; as a result, the most prevalent cause of chronic hepatic disease in hemophilia patients is hepatitis C. Hepatitis C virus is mainly transmitted through blood and its products. Once the hepatitis B virus was identified and all blood infected with hepatitis B virus was consequently purified, the most common cause of hepatitis after blood injection became a non-A non-B hepatitis -later given the name hepatitis C.

It is worth noting that the hepatitis C detection test was introduced in 1990 and then in 1992, and medical experts then managed to reduce the risk of the transmission of hepatitis C to blood recipients, especially to hemophilia patients, through identifying infected blood and their elimination. The fight against the disease started with the thermal inactivation of viruses in blood products and the subsequent use of organic solvents in 1985. These efforts significantly reduced hepatitis C but were not fully effective. With the increasing advances in virus inactivation methods, the cause of hepatitis C was eventually discovered. Coagulation factors are usually prepared using several units of blood (120-1000 units) and the risk of infection is higher in coagulation factors compared to just one unit of blood.

In the first study conducted on Iranian hemophilia patients in 1996, the prevalence of hepatitis C was 61% in the 200 hemophilia patients examined using the ELISA method. The prevalence of hepatitis C in hemophilia patients appears to be 45% in certain areas of Iran and over 70% in others. The rate of infection with hepatitis C is higher in older patients, who have received more coagulation factors.

? In which type of hemophilia (A or B) is hepatitis C more prevalent?

According to previous studies, infection with hepatitis C is higher in patients with hemophilia A than in patients with hemophilia B due to the higher amount of coagulation factors received by hemophilia A patients.

? Is the risk of infection with hepatitis C higher with the use of coagulation factors or with the use of fresh plasma?

The use of coagulation factors is associated with a higher risk of infection with hepatitis. The reason is that coagulation factors are made of several units of blood while fresh plasma is drawn from only one patient. In general, the lowest rate of infection with hepatitis C is seen among patients who use cryoprecipitate and the highest rate of infection in patients who use coagulation factor VIII. The use of effective virus inactivation and donor screening methods has reduced the risk of infection with hepatitis C virus to a great extent today. In over 85% of the cases, hepatitis C virus remains in the

body and continues its activities; however, the disease progresses very slowly and becomes chronic (cirrhosis) in only 30-40% of the cases.

A large number of hemophilia patients also suffer from HIV. HIV exacerbates liver diseases through decreasing the functionality of the immune system, which facilitates the proliferation of the hepatitis virus.



About 20% of hemophilia patients with an anti-HCV antibody (HCV Ab+), normal liver enzyme levels (ALT levels), and no virus found in the PCR blood test have been able to fully excrete the virus from their body and need not be worried.



Can hemophilia patients with hepatitis C receive an interferon-alpha injection for treatment?

Yes; Interferon-alpha can be injected to patients who need this treatment; however, newer medications are more effective.

? **Is liver biopsy necessary for hemophilia patients with hepatitis C?**

Biopsy is an appropriate guide for deciding whether or not the patient with hepatitis C should be treated. Although liver biopsy can be performed on hemophilia patients in compliance with certain principles, it should be refused due to the potential risks it poses (for instance, 2 cases of death reported in a study conducted by Aledort). Decision about treating the patients is made with the help of liver tests, PCR, liver and spleen scan, ultrasound and fibroscan. Liver biopsy has been outdated with the introduction of fibroscan and measuring the disease progression with periodical fibroscans is a new possibility.

? **Are hemophilia patients at risk of bleeding after receiving an interferon-alpha injection?**

No; there are no restrictions against the subcutaneous injection of interferon-alpha to hemophilia patients. However, the new oral antiviral therapies introduced to the market obviate the use of interferon.

? **I have three sons, aged 3, 9 and 15, all suffering from hemophilia. My 15 year-old and 9 year-old have been infected with hepatitis C. Their blood tests have shown an increase in the liver**

enzymes (ALT disorder), and their PCR tests have shown positive HCV RNA; but the physician prescribed treatment with interferon-alpha only for my 15 year-old and left my 9 year-old without any treatments. What do you think of these prescriptions?

Various factors are involved in making decisions about whether or not hemophilia patients with hepatitis C should be treated. The main factor is the presence or absence of clinical symptoms of a liver disease. Other factors include the presence or absence of a liver enzyme disorder, the liver ultrasound, the liver and spleen scan, the presence of virus in the blood (PCR), the liver fibrosis status in the fibroscan and age.

Some researchers suggest starting the interferon-alpha treatment for hemophilia patients with hepatitis C only after the age of 12 and advise physicians to avoid its prescription to younger patients. You should not worry because the disease progresses very slowly, and delay in the treatment of your son does not add to the severity of the problem. Regardless, I recommend starting the treatment if and only if the liver enzyme disorder persists (proved by several tests) and the virus is present in the blood (HCV RNA in the PCR test). You can have an effective role in controlling your child's disease by better understanding the disease and the treatment objectives.

? **How different is the effect of interferon-alpha in treating hepatitis C in hemophilia patients and non-hemophilia patients?**

Given that hemophilia patients frequently use blood and its products, it is possible for them to have several types of hepatitis C virus in their body and interferon-alpha is therefore less effective in them.

? **Is a positive HIV test in hemophilia patients a barrier against the use of interferon-alpha for treating their hepatitis C?**

No.; these patients can receive interferon-alpha injections, but its effect will be lower than in the HIV-negative patients.

? **I am a man of 25 with hemophilia and hepatitis C. All the liver tests, liver and spleen scans, abdominal ultrasound, etc., have showed normal results. Should I receive any treatments?**

According to the most recent medical findings, patients with hepatitis C who get normal liver test results on several occasions and who do not suffer from a severe liver damage according to their fibroscan do not need any antiviral treatments at the moment and can wait for newer medications. However, the final decision should be made by your physi-

cian, and given that science is constantly moving forward, your physician's decision is also subject to change in the future.

? Is endoscopy necessary for all hemophilia patients with hepatitis C?

No; performing an upper endoscopy for examining the presence of varicose veins (swollen veins) in the esophagus is not recommended for patients younger than 20. Patients with at least 20 years of infection with hepatitis C, or at least 35 years according to some studies, should undergo endoscopy before beginning their treatment with interferon-alpha.

Liver transplant is a specific procedure for the treatment of liver failure at highly advanced stages. Fewer than 50 cases of liver transplant have been reported for hemophilia patients with liver failure caused by their infection with hepatitis C. The majority of hemophilia patients with hepatitis C are not at high stages of the disease and pharmacotherapy can be effectively used for their treatment. However, even if a liver transplant is necessary, it cannot be easily performed in Iran and sending the patient abroad for the transplant is very expensive. If the liver transplant is successful and the liver is improved, the coagulation factor deficiency is also resolved in most patients and recovery from hemophilia is also achieved. The patient's HIV results should be negative before carrying out the liver transplant. The long-term results of performing liver transplants for hemophilia patients are yet to be determined.

► Hemophilia patients and hepatitis A

Hepatitis A is a type of liver disease. The disease pathogen is a tiny virus 27 nm in size. The molecular structure of the virus is fully identified. As of yet, only one genotype of this virus has been introduced. Hepatitis A is more prevalent in countries with rather poor levels of hygiene and low-standard potable water, and is thus more commonly seen in Southern and Eastern Europe, Africa, the Middle East and the Far East. The prevalence of hepatitis A is also considerable in Iran.

Hepatitis A virus is transmitted orally (through infected water or food) and the spread of the disease is associated with overcrowding, poor hygiene and the lack of proper sewage disposal. With the improvement of health conditions, the global incidence of the disease is decreasing.

Scientifically, the risk of the transmission of hepatitis A through the injection of blood and its products is negligible. Given that most patients are infected at a young age, hemophilia patients might also be infected with hepatitis A.

Symptoms of infection with hepatitis A are similar to symptoms of infection with other types of hepatitis and include cold (flu-like) symptoms, diarrhea, abdominal pain, anorexia, nausea, a feeling of general malaise, headache, mild itching, dark urine and jaundice.

Hepatitis A is resolved by itself and the virus is fully excreted from the body. Hepatitis A does not have a carrier state.

Considering that infection with hepatitis A in hemophilic patients with hepatitis C may cause severe hepatic diseases, hemophilia patients are advised to immunize themselves against hepatitis A in addition to respecting the codes of hygiene, such as consuming safe potable water and food and respecting personal hygiene in order to inhibit the exacerbation of their hepatic diseases.



Attention

The potential transmission of infectious agents still limits the safe use of blood and its products. The virus inactivation of blood products is a desire that is not always practical. Reducing this risk to a good level will therefore be efficient. Simply expressing that blood is infected does not solve the problem and instead makes people skeptical toward the use of blood and its products, which will ultimately affect the patients more than any other group

There is a religious sect in the US that does not allow the blood transfusion based on its beliefs, resulting even in the death of some of its members. If we propagate the infection of blood sup-

To hemophilia patients

plies, can we expect hospitals to admit patients for blood transfusions? Wouldn't the prevention of patients from receiving blood caused by false propagations threaten their life? We need to think more logically and act reasonably. The health of the entire society is a priority. The prevalence of hepatitis C is lower in Iran than in western countries. If blood supplies are evaluated, the blood supply collected in Iran can be safer than foreign supplies. As for coagulation factors, it is necessary to perform different stages of the virus inactivation procedure to purify blood products in addition to testing them for different types of hepatitis. The selection of suitable (and not professional) blood donors can help produce safer blood and blood products, which is especially practical in Iran since the majority of blood donors in the country donate their blood for good will. It should be noted that all these measures do not negate the authorities' responsibility toward observing the global standards in the preparation and distribution of blood and blood products (including the factors).



Which transmission route of hepatitis C is more common among hemophilia patients?

As already noted, the use of blood and its products (such as fresh plasma) before 1995-1996 counts as a major route for the transmission of hepatitis C to hemophilia patients. Although there are other hepatitis C transmission routes, including high hospitalization frequency, frequent injections, dental procedures, intravenous drug addiction and sexual promiscuity, hemophilia patients are not commonly infected with hepatitis C through intravenous drug addiction and sexual promiscuity, as the 6 year-olds and the 10 year-olds with hemophilia are not to be doubted with respect to these behaviors.

The risk of the transmission of hepatitis C from infected mothers to their children is lower than 5%, and given that hepatitis C has a very low prevalence rate in the society (about 0.3%) and given that it is highly prevalent among hemophilia patients, this transmission route does not commonly apply to hemophilia patients with hepatitis C.


In general, the use of blood and its products, coagulation factors (foreign and local; if not virus-inactivated), frequent hospitalizations and frequent injections due to the need for blood and its products are major causes of infection with hepatitis C in hemophilia patients.

The problems with which hemophilia patients with hepatitis C are faced can be solved by paying more attention to their treatment through providing more accurate diagnostic facilities and more effective medications, improving the public services of the Blood Transfusion Organization and advertising effective blood donation.

? Does the use of recombinant coagulation factors reduce the risk of the transmission of infections to zero?

There is still a risk of the transmission of infections due to the use of human plasma albumin in the production of these coagulation factors; however, it is reduced to a great degree. The use of gene therapy in the future will eliminate the risk of the transmission of infections through treating hemophilia patients and obviating the need for using coagulation factors.

Parents of hemophilia patients with hepatitis should not forget the importance of providing emotional support to their child. They should not contribute to a greater isolation of the child in the family and at school through setting unnecessary limitations and openly expressing that their child has hepatitis. There is no need to inform other members of the family, the school authorities and the classmates of the child's infection. Given that the disease is usually transmitted through the blood, no risk threatens these individuals. Only when the child receives interferon (as per the physician's order), fatigue, impaired concentration and other side effects justify informing the school authorities and teachers.



Don't forget!





A Comprehensive Guide For Hepatitis C

CHAPTER 07

To thalassemia patients

Thalassemia is a relatively common hereditary anemia that is controlled through regular blood transfusion and the use of iron-chelating agents (Desferal). The treatment aims to keep hemoglobin at the 10 g/dl level. Liver enzyme disorders are common among thalassemia patients. One of the significant side effects of blood transfusion is the transmission of viral infections, including hepatitis B and C and HIV.

Based on the available statistics, 20-30% of thalassemia patients in Iran suffer from hepatitis C.

Given the increased longevity of thalassemia patients, liver disorders become more common in this group of patients every day. However, the major cause of liver enzyme disorders is excessive iron deposition, which particularly worsens after splenectomy. The proper use of desferal can reduce iron deposition in the liver. It should be noted that iron overdose may exacerbate the effects of hepatitis C on the liver. When there is an excess of iron in the liver, the hepatitis-C-inhibiting effects of interferon decrease, which is why specialists recommend the treatment of iron overdose with desferal and frequent serum ferritin measurements for determining iron levels first.

Patients with thalassemia are at a risk of infection with hepatitis B and should receive hepatitis B vaccination.



The use of peginterferon and ribavirin may exacerbate anemia in thalassemia patients; however, if ribavirin is not administered, peginterferon alone is less likely to counteract the disease.

New oral antiviral drugs might have the potential to treat 100% of the patients.



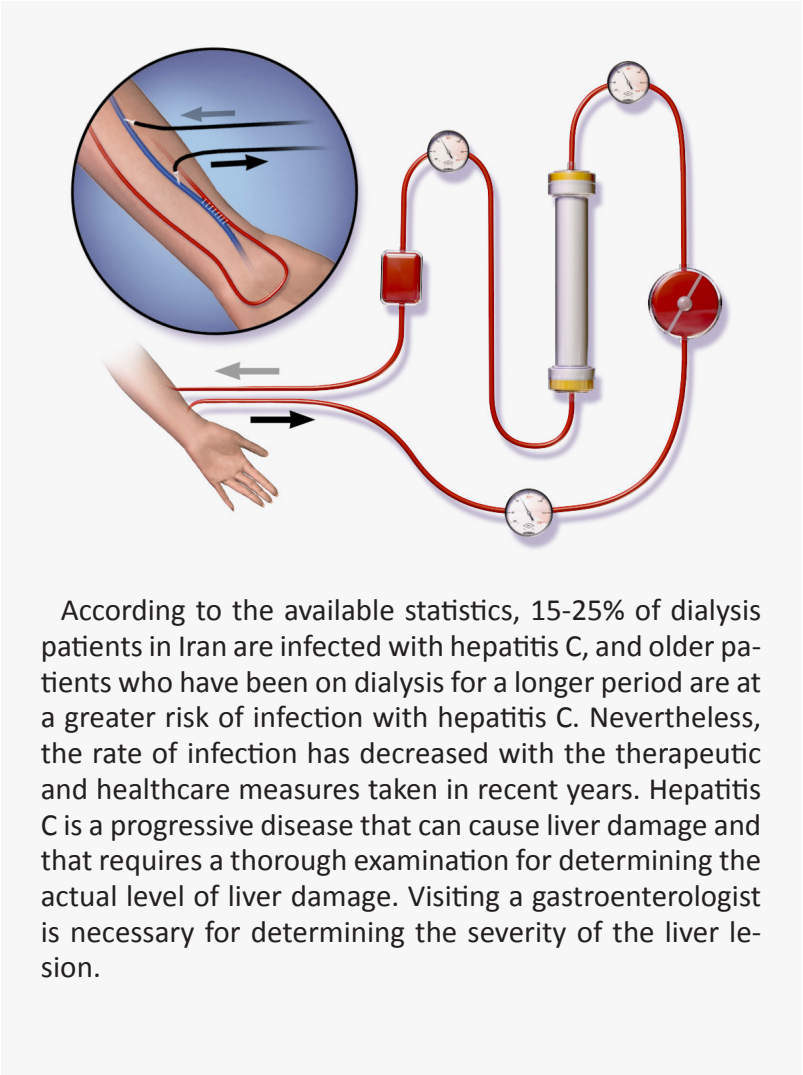
A Comprehensive Guide For Hepatitis C

CHAPTER 08

To dialysis and kidney transplant patients

Patients on hemodialysis (due to kidney failure) are exposed to the risk of infection with hepatitis C. These patients get blood transfusions because of their anemia and, as already noted, blood supplies were not tested in the past for hepatitis C. These patients may also get infected with hepatitis C during hemodialysis and in contact with infected blood.

To dialysis and kidney transplant patients



According to the available statistics, 15-25% of dialysis patients in Iran are infected with hepatitis C, and older patients who have been on dialysis for a longer period are at a greater risk of infection with hepatitis C. Nevertheless, the rate of infection has decreased with the therapeutic and healthcare measures taken in recent years. Hepatitis C is a progressive disease that can cause liver damage and that requires a thorough examination for determining the actual level of liver damage. Visiting a gastroenterologist is necessary for determining the severity of the liver lesion.

? Should the dialysis machine be separated for patients with hepatitis C?

No; according to the instructions of the World Health Organization, there is no need to separate dialysis machines used for patients with hepatitis C; however, respecting the codes of hygiene, proper washing of the dialysis machine and preventing the patients' contact with each other's blood are absolutely necessary. These precautions necessitate the separation of blood pressure recording devices, nurses' frequent replacement of their gloves and a properly cleaned physical environment in order to prevent the transmission of hepatitis C more effectively.

There is no need to separate dialysis machines used for patients with hepatitis C.



? Do dialysis patients with hepatitis C get kidney transplants?

Yes; however, certain tests need to be taken for examining the patient's liver condition. Liver biopsy is required before the transplant. If the tests yield extreme results, kidney transplant cannot be performed, and treatment with interferon will then be essential for inhibiting hepatitis C. The PCR results have to be negative in order to perform the transplant.

► Risks following kidney transplant

Given that patients should use immunosuppressant drugs such as Cyclosporine, Sandimmune, Prednisolone and Azathioprine after their kidney transplant to protect the transplanted kidney, there is a risk of the exacerbation of hepatitis and liver lesions. The patients should therefore regularly visit a gastroenterologist for the evaluation of their liver condition. In general, patients should get follow-up examinations, liver ultrasounds and routine liver functioning tests (measuring SGOT and SGPT) for a few years after the transplant; however, performing periodical liver biopsies or fibroscans is necessary for three years after the transplant in order to determine the liver condition and adjust the medication regimen.



In the case of failure to visit a physician in time and the exacerbation of the liver damage, the liver might fail and no treatments might then fall effective.



A Comprehensive Guide For Hepatitis C

CHAPTER 09

Hepatitis C and cancer

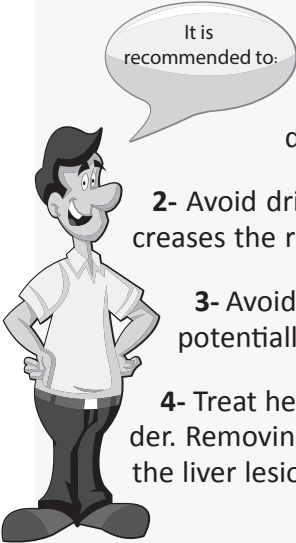
Cancer refers to the abnormal uncontrollable growth of body cells that destroy normal cells. Cancer is in fact the uncontrollable proliferation of cells. Liver, one of the largest organs of the body, can also become cancerous. Liver cancer is more prevalent in Africa and Asia, particularly in Southeast Asia, Japan and China. The disease often affects men, especially men over the age of 50.

Causes: The main known causes of primary liver cancer include cirrhosis (lazy liver), chronic hepatitis B and C viral infection, alcohol consumption and aflatoxin consumption. Cirrhosis (lazy liver) occurs with the progression of hepatic inflammation, destruction of the liver tissue and its scarring.

► Hepatitis C and liver cancer

Researchers have found that infection with hepatitis C is a major cause of liver cancer, which is especially true in Japan, Italy, Spain, South Africa and the US. About 5% of the patients with hepatitis C who also suffer from a lazy liver will be affected by liver cancer, normally taking several years to appear. Patients infected with genotype-1b hepatitis C will be affected by a more severe disease and will be at a higher risk of liver cancer. The incidence of liver cancer is necessarily preceded by cirrhosis (lazy liver). Naturally, not all the patients with hepatitis C are affected by liver cancer; older individuals, often older men, who continue drinking alcohol or who are also infected with hepatitis B are more commonly affected by liver cancer.

Early symptoms of liver cancer are non-specific and include weakness and anorexia; however, in advanced stages, symptoms of the disease include jaundice and ascites. For an early diagnosis of liver cancer, periodical alpha-fetoprotein (aFP) blood tests (according to the physician's order) and abdominal ultrasounds are essential.



It is recommended to:

1- Avoid smoking: Smoking is a pre-disposing factor for cancer.

2- Avoid drinking alcohol: Alcohol consumption increases the risk of liver cancer.

3- Avoid using stockpiled peanuts and pistachios potentially infected with aflatoxin.

4- Treat hepatitis C according to the physician's order. Removing the virus and reducing the severity of the liver lesion can prevent cancer.

► Treatment

Current treatments for liver cancer include the surgical removal of the tumor, hepatic artery chemotherapy together with embolization, or a liver transplant, which requires the early diagnosis of liver cancer. The risk of recurrence is rather high. One therapeutic procedure used is to inject pure alcohol into the tumor, which kills the cancer cells.

► What is chemoembolization?

Chemoembolization is a combination of the topical release of the chemotherapy drug after injection into the hepatic artery and the subsequent blockage of the artery supplying blood to the tumor. Through this method, tumor-destroying drugs are directly injected into the artery supplying blood to the tumor and therefore stop the tumor growth. This procedure is performed by a radiologist expert in vascular conditions.

After their discharge, patients should rest for a longer period and may experience abdominal pain, fever, nausea and vomiting, which should be reported to their physician. It should be noted that this procedure stops the tumor growth only in two-thirds of the cases and that its number of repeats should be arranged with the physician.

► Interferon and liver cancer

Numerous studies have shown that a lazy liver and liver cancer are less likely to occur in patients being treated with interferon.

Alpha-fetoprotein (aFP) blood test should be periodically performed during the early stages.

► What is Nexavar?

Nexavar or Sorafenib is a small molecular inhibitor of cancer cell proliferation. This medicine inhibits the tyrosine kinase receptors in the blood vessels and prevents the supply of enough blood to the cancer tissue. Patients should learn about the side effects of the medication prior to starting its consumption and should consult with a physician about their right doses.



- Key points that should be checked about the patients before starting the treatment include:

- Any type of allergies;
- Any heart conditions or a history of chest pain;
- A history of blood pressure;
- Renal disorders;
- Urinary disorders.

- This medication should not be taken during pregnancy and patients should use contraception methods while under the regimen.

► Instructions for use

The usual dose of the medication is 2 tablets twice a day (usually 4 tablets a day) according to the physician's instructions and the patient's tolerance levels. The medication should be taken whole with water and not with food. If two doses of the medication are missed, that dose is left out and the next dose is still taken according to the set schedule.

► Side effects

Side effects of this medication are divided into the hazardous and the non-hazardous categories:

- Decreased blood flow to the heart and heart attack: Contact your physician and the emergency department immediately in case of experiencing chest pain, shortness of breath, dizziness, nausea and vomiting accompanied with excessive sweating.

- Bleeding: The use of this medication increases the risk of bleeding.

- Hypertension: Blood pressure should be measured ev-

ery week during the first 6 weeks of taking the medication and any hypertension should be treated.

○ Skin complications: Erythema, pain, swelling and blisters on the palms and soles are serious complications.

Under such conditions, the physician will change the medication dose.

- Medical recommendations for reducing skin reactions

○ Avoid contact with hot water when washing dishes or bathing;

○ Avoid contact with strong chemicals found in household cleaning products;

○ Avoid exposure to heat, including in the sauna or while sunbathing or sitting in front of sunny windows;

○ Avoid activities causing foot abrasion; for instance, jogging, aerobic exercises and long walks;

○ Avoid activities causing hand abrasion, such as using tools that require the pressing of the hand against a hard surface; for instance, gardening tools, knives and screw-drivers.

- Recommendations for reducing the severity of the side effects

- Use creams and moisturizers, such as Nivea and Eucerin;
- Use ice packs or cold compresses indirectly on hands and feet for 20 minutes each time (avoid putting the ice directly on the skin);
- Keep hands and feet up when sitting or lying down;
- Avoid rubbing the skin with the towel for drying after a shower. The towel should touch the skin very gently to soak up the water;
- Wear loose-fitting clothes and shoes;
- Wear soft shoes;
- Moisten the damaged skin in a magnesium sulfate and water solution;
- Apply moisturizer after showering and bathing;
- Wash the scalp and the body with anti-dandruff shampoos.



- A recommendation for remedying fatigue

Fatigue is the most common complaint among cancer patients. Regular physical activities are recommended in addition to an afternoon sleep and enough rest. Patients should entertain themselves with games, music, books, etc.



A Comprehensive Guide For Hepatitis C

CHAPTER 10

Treatment

After the diagnosis of hepatitis C and upon visiting a specialist, the patient is asked questions that help predict the approximate time of infection with the disease. The physician takes various factors into account for the treatment of the patient, including age, gender, liver enzymes status, viral replication status (through the PCR test), severity of liver damage in the liver biopsy or the fibroscan and the virus genotype. The patient will also pose many questions about the treatment and its outcome, to which the physician should respond. The patient should feel at ease with his physician, and the physician should respond to the patient's questions with patience.



Do all patients with hepatitis C need to be treated?

This question needs more investigations. An antiviral treatment aims to clear the blood of the virus and to consequently prevent more damage to the liver. When the severity of the liver damage is more moderate, the patient can wait for newer more effective medications to enter the market.

► Old treatments

At the present moment, it is not possible for all patients with hepatitis C residing in developing countries to undergo treatments with the new oral antiviral medications; as a result, peginterferon alpha and ribavirin are still used for the treatment of hepatitis C.

► What is interferon?

Interferon is a protein naturally made by the cells in response to viral infections, including viral hepatitis, and counts as the body's defense against these infections. Patients with chronic hepatitis C appear to have difficulty



producing normal levels of interferon and therefore develop an internal interferon deficiency.

Interferon was discovered in 1957 by scientists conducting research on viruses. They found a matter that inhibited virus replication. The first interferon introduced to the market was made of human white cells, the production of which was a technical hassle, therefore supplied in small amounts. Genetic technologies made the production of interferon in large amounts feasible.

There are various types of interferons, including alpha, gamma and all kinds are protein. Interferon-alpha, which has two types including 2a and 2b, has antiviral effects on hepatitis C. Interferon enhances the immune system (body's defense) and consequently fights the hepatitis C virus. Through inhibiting virus replication, this medication stops the progression of the liver lesion. Another advantage of interferon is the inhibition of abnormal cell proliferation and the reduction of fibrosis (scarring) of the liver. Interferon is available in the market in two types including Pegasys and PegIntron, which are injected every two weeks.

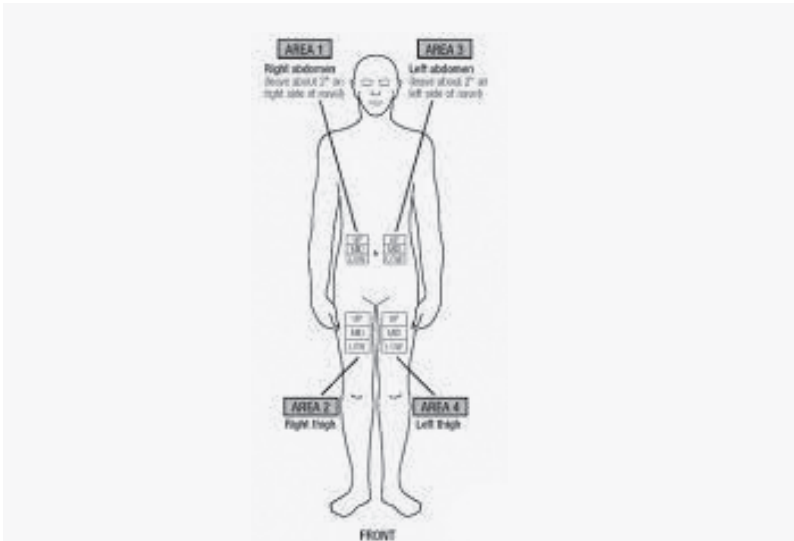
Peginterferon is prepared as shots containing either solutions or powders that need to be dissolved in distilled water before injection. The medication is administered subcutaneously using a special syringe made for insulin injection. The injection sites can be determined according

to the following figure and the medication can then be injected in different sites in rotation. Most people quickly grasp the proper methods of injection. The injection is preferred to be performed by either yourself or a family member, as injection nurses are not always around.



? Which patients are given a priority for treatment with peginterferon and ribavirin?

When hepatitis C virus is positive in the PCR test, the blood platelets are over 70 thousand per microliter, white cells over 3 thousand per microliter and hemoglobin over



11 g/dl, and blood coagulation is normal, an antiviral treatment is necessary, and these medications are then used if newer medications are not available.

The response to treatment is more favorable in patients under the age of 30 who are infected with hepatitis C virus genotypes 2 and 3 for whom cirrhosis has not yet occurred, and when the virus count is lower than 2 million copies/ml and the patients do not drink alcohol. The physician cannot predict the effectiveness or ineffectiveness of the treatment by a hundred percent before starting the treatment. The type and genotype of the hepatitis virus affect the level of responsiveness to the treatment. The first genotype of the virus (1a and 1b) is more invasive

and severe and results in a less favorable response to peginterferon.

Peginterferon is administered in two types: 2a or Pegasys, injected at the dose of 150 µg per week; and 2b or PegIntron, administered based on the patient's weight (according to the physician's instructions).

- ***Keep peginterferon refrigerated but not frozen.***
- ***In case of missing one dose, ignore it and do not double the next dose.***

The treatment lasts six months (24 weeks) for genotypes 2 and 3, and twelve months (48 weeks) for genotypes 1a and 1b. Based on the physician's recommendations, the duration of the treatment may be increased or reduced to enhance the effectiveness of the medication.

? How can we tell if the hepatitis C treatment has been effective?

About 50-60% of the cases with hepatitis C respond well to antiviral treatment with peginterferon alpha and ribavirin, which is ascertained when the liver enzyme levels become normal, the virus is removed from the blood and the PCR result is negative. In many cases, the severity of liver damage is reduced with the elimination of the virus.

The most favorable response to the treatment is achieved when the liver enzyme levels remain normal and the PCR result remains negative 6 months after the termination of pharmacotherapy. Patients are recommended to follow up with their physician about their disease for a few years. The different effectiveness of treatment with interferon in different countries appears to be due to the different types and genotypes of the virus present. Different responses to the treatment can even be noticed in different parts of a country. The physician can better predict the effectiveness or ineffectiveness of the treatment before starting it through the IL28B polymorphism test. During the treatment, the physician can figure out the level of responsiveness to the treatment and its side effects through performing special tests and studying their results. Nevertheless, regular periodical performing of the tests is necessary.

? Can we tell of the effectiveness of the interferon treatment at the beginning of the treatment?

Yes; although treatment lasts twelve months, an intense drop in virus load in the blood in the initial weeks of the treatment shows a favorable response to the treatment. However, if the level of liver enzymes remains normal and the virus activity in the blood is negative (in the PCR test) 6 months after the termination of pharmacotherapy, the response to the treatment can be taken as optimum and

the virus can be said to have been fully eliminated from the blood. Some researchers believe that if the response to medication is not favorable in the first three months of the treatment, the useless treatment should be discontinued.

? **How can we tell if interferon has been effective or ineffective for patients with chronic hepatitis C?**

The effect of the medication can be determined in patients through periodical liver tests, the PCR and another liver fibroscan.

- The following patients show a more favorable response to interferon:

- 1- Patients under the age of 30;
- 2- Patients without cirrhosis in their liver biopsy;
- 3- Patients with hepatitis C virus genotype 2 and 3 (all except genotype 1);
- 4- Patients with fewer than 2 million RNA viruses per milliliter;
- 5- Patients with liver enzyme levels twice the normal;
- 6- Patients not drinking alcohol.

The physician cannot predict the effectiveness or ineffectiveness of the treatment before starting it. The type



and genotype of the hepatitis virus affect the level of responsiveness to the treatment. Genotype 1 of the virus (1a and 1b) is more invasive and severe and responds less favorably to interferons.

► **Necessary steps to take before starting treatment with interferon**

Performing blood tests before starting the treatment is necessary for examining the thyroid gland functioning. It is also necessary to examine the virus in the blood through the PCR test and liver tests (for alkaline phosphatase, Gama GT, AST and ALT), prothrombin time [PT], albumin, abdominal ultrasound, liver biopsy (in non-hemophilic patients), eye exam and psychiatric consultation.

► Necessary steps during the interferon treatment

Frequent examinations and blood tests for examining liver enzymes (ALT and AST), blood count, thyroid and PT should be performed during the treatment. If the liver enzyme levels become normal, the effectiveness of the medication is fully ascertained; however, if the liver enzyme levels do not become normal, the ineffectiveness of the medication is not definite. The physician will recommend another liver biopsy if necessary.

- The following patients should not take interferons:

- 1- Patients at advanced stages of lazy liver (cirrhosis), detected by ascites, the presence of prominent blood vessels in the esophagus (esophageal varices) and dizziness; interferon may exacerbate the disease in these patients;
- 2- Patients with symptoms of severe nervous disorders, especially those with severe depression or failed suicide attempts;
- 3- Patients with a kidney transplant;
- 4- Patients with extremely low levels of blood platelets and white cells;
- 5- Patients who continue drinking alcohol;
- 6- Patients who continue their intravenous drug addiction;
- 7- Pregnant and breastfeeding women;

- 8- Patients with advanced cardiac and pulmonary diseases;
- 9- Patients over the age of 60;
- 10- Patients with psoriasis.

▶ **Newborns and infants**

Hepatitis C is common in children with hemophilia and should be properly resolved. Given that the risk of mother-infant transmission of hepatitis C is very low, the number of children with hepatitis C is also low. Furthermore, newborns who have already undergone exchange transfusion due to their jaundice are at the risk of infection with hepatitis C and should be checked for signs of the disease.

Few studies have been conducted on the use of interferon in infants with hepatitis C. The use of interferon in patients under the age of 13 has not been approved by all health centers; however, the key point is that patients under 10 are preferred to not be treated with interferon and to stay hopeful to the future, as hepatitis C does not cause serious liver damage in patients under the age of 10. Waiting for better medications then becomes an option.

▶ **Side effects of interferon**

The side effects of interferon tend to appear more severely at the beginning of the treatment and with the ini-

tial doses. The primary side effects include flu-like symptoms, such as fever and chills, muscular pain, malaise, fatigue and headache, which normally begin 6-8 hours after the injection and last for hours and then disappear. The severity of these side effects can be reduced by taking an acetaminophen codeine one hour before the injection. Symptoms often disappear with persistence in taking interferon. It should be noted that not all patients show these symptoms and many can tolerate the medication without any side effects. The side effects of interferon include fatigue, soreness, mood change, impaired thinking, hair loss, hair loss, headache and skin irritation at the site of injection. Uncommon but serious side effects include thyroid gland disorders and ocular complications. It should be noted that the number of white cells and platelets decreases due to the reduced bone marrow activity and patients should therefore be regularly followed up with.

- 1- Hair loss is usually mild and the hair gradually returns to its normal state after ending the treatment with interferon. There is no need to worry about this side effect.
- 2- The side effects of interferon are exclusive to its use and will disappear after ending the treatment.
- 3- Taking an acetaminophen codeine or ibuprofen before the overnight injection of the medication can reduce its side effects. The physician reduces the medication dose in 15% of the patients and

stops it in 5% due to its side effects.

4- Given that most patients with hepatitis C do not present any symptoms (until the final stages), patients tend to complain about experiencing more side effects than actual disease symptoms when first starting the treatment



► Ribavirin

Ribavirin has great effects on viruses and was confirmed in 1988 by the FDA for use along with interferons in patients with hepatitis C. Ribavirin cannot fully eradicate the disease; however, it reinforces the effects of interferon. Although the exclusive use of ribavirin can normalize liver enzyme levels, it does not have any effects on virus activity and is therefore useless. Ribavirin is manufactured as

100-200 mg capsules or tablets. The recommended daily dose of the medication is 600-1200 mg and varies with the patient's weight and virus genotype.

► Side effects of ribavirin

One major side effect of ribavirin is the early destruction of white cells, followed by anemia. This side effect can easily be dealt with through performing frequent tests. The physician may decide to reduce the medication dose or to temporarily stop it at certain stages of the treatment and patients should not worry about this side effect.

Other side effects of ribavirin include itching, shortness of breath and skin lesions. Please contact your physician in case of experiencing lethargy, anemia and dark urine with the use of ribavirin.

Patients with anemia or kidney dysfunction (and those on hemodialysis) cannot tolerate ribavirin. The use of ribavirin during pregnancy has serious side effects on the fetus or embryo and all women using ribavirin are therefore recommended to be careful about getting pregnant and to fully stop the medication in case of suspected pregnancy.

Meanwhile, men using ribavirin should refrain from impregnating their partner. The advices forbidding pregnancy hold for up to 6 months after ending the medication

treatment. Combination therapy (with interferon and ribavirin) increases the chance of removing the virus from the body and prevention of the exacerbation of the liver damage and 40-50% of patients respond well to the treatment.

There is a prohibition against the use of ribavirin during pregnancy. Both spouses should use methods of contraception to ensure their safety. It is always good to have a second string to your bow!



Is there a chance of disease recurrence after stopping the treatment?

Yes; the virus may re-appear in the blood after the liver enzyme levels have become normal and the PCR result has become negative. The disease is then said to have recurred. The risk of disease recurrence is always present. The virus can hide in the white cells or the liver cells and become active for an unknown reason. However, if the PCR result remains negative 6 months after the termination of the treatment, the risk of recurrence in the future will be very low and the patient can consider himself treated.



Can cases of acute hepatitis C be treated?

If the acute hepatitis caused by hepatitis C virus is diagnosed early, it can be easily treated and is eradicated in over 95% of the cases.

► New treatments for hepatitis C

The history of the diagnosis and treatment of hepatitis C since 1991 indicates the focus of researchers and the pharmaceutical industry on the inhibition and eradication of this virus.

In the early years, the 3-million-units interferon-alpha was exclusively used to treat hepatitis C and had the effect of eliminating the virus only in 20% of the cases. After antiviral ribavirin tablets were introduced and added to the treatment and then with the discovery of peginterferon injected weekly, about 50% of the cases were successfully treated. New medications such as Teleprevir and Boceprevir were introduced to the market in the last decade. The use of these medications in combination with peginterferon and ribavirin has increased the chance of eradicating the hepatitis C virus genotype 1. Nevertheless, these medications have side effects that pose limitations to the treatment of hepatitis C.



► **What happened in 2014?**

Hepatologists once dreamed of eradicating the hepatitis C with antiviral pills without resorting to interferons. This dream first came true with the introduction of Sofosbuvir in 2014 and its approval by the FDA, which is in charge of examining and approving all medications used in the US and in other developed industrial countries. This new medication then paved the way for the introduction of other medications to the market, which will be examined in this chapter

Note: You should discuss the information provided in this chapter with your physician only and avoid self-medication at all costs.

The following points are important in making decisions for the treatment of hepatitis C:

- 1- The level of liver damage defined by fibrosis; that is, the presence or absence of fibrosis and its severity detected by a liver biopsy or fibroscan.
- 2- The level of liver damage detected through clinical symptoms (the presence or absence of an enlarged spleen and ascites or accumulated fluid in the abdomen), blood coagulation disorders and the blood platelet count.
- 3- The virus genotype –which is either 1 or not.
- 4- The patient’s age and the presence or ab-

sence of disabling diseases, such as heart disease, uncontrolled diabetes, high blood pressure, mental problems, etc.

► Sofosbuvir

Sofosbuvir is a nucleotide analog inhibitor of hepatitis C virus NS5B polymerase. It is used for all genotypes. This medication is excreted by the kidneys and can be used along with ribavirin for 12-24 weeks in the treatment of genotypes 2 and 3 of hepatitis C without the use of interferons.

For genotypes 1a and 1b, sofosbuvir is used along with peginterferon alpha and ribavirin for 12-24 weeks.

Sofosbuvir is a 400-mg tablet that should be used daily and that is excreted by the kidneys. In addition, it presents very few side effects. No resistance to the medication has been reported. The medication has no side effects such as fatigue, headache, insomnia, anemia and skin lesions.

► Ledipasvir

Ledipasvir is an inhibitor of hepatitis C virus NS5A polymerase that exerts its antiviral effects on genotypes 1a



and 1b only. This medication is used in combination with sofosbuvir under the name Harvoni. Ledipasvir is produced in 90-mg doses.

Harvoni®

Harvoni® can be used in all genotypes of hepatitis C and all stages of liver disease (even with cirrhosis). It can eliminate HCV in 98 percent of cases. Contrary to pegylated interferon alpha, which has numerous severe adverse effects, Harvoni® does not have significant side effects. Fatigue and headache are its most common side effects. Diarrhea, nausea and insomnia are some other side effects. Harvoni® can be taken with or without food.

Precautions:

- The duration of treatment with Harvoni® (12 or 24 weeks) is determined based on severity of the disease (presence or absence of cirrhosis), and history of previous anti-viral medication and its response.
- Harvoni® has been studied and approved for use in adults over 18 years of age. No official reports have been published on the efficacy and safety of this medication in children under 18 years old.

- Harvoni® is not recommended in people with hepatitis C undergoing dialysis.
- Harvoni® is not allowed during pregnancy [and breast-feeding].
- It is recommended not to discontinue Harvoni® abruptly and without physician's advice.
- If you miss a dose (which should be totally avoided), the next dose should not be doubled.

Drug interaction

The most important point about Harvoni® is its interaction with other drugs, which might be life threatening in some cases.

- If you are a cardiac patient and use Amiodaron, you may develop severe symptomatic bradycardia (reduced heartbeat) if you take Harvoni® simultaneously.
- Serum level of Ledipasvir reduces if taken with an antacid containing AlOH or MgOH. It is recommended to take the antacid 4 hours before or after Harvoni®.
- Harvoni® increases serum level of digoxin (a heart medication), which needs attention.

- Taken with Harvoni[®], Losuvastatin (used for controlling blood lipids) can increase serum levels of the drug, and increase the risk of myopathy (muscle damage).

NB

Given the possibility of drug interaction, you are strictly prohibited from taking any medications, even herbal medicine, without physician's prescription.



► Viekira Pak

Viekira Pak is a combination of 4 medications, including Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir. Viekira Pak is used by itself or in combination with ribavirin only for cases with genotype 1 and for a period of 12-24 weeks with an effectiveness reaching 100%.

► Treatment of chronic hepatitis C genotypes 1a and 1b

These genotypes of hepatitis C can be treated with peginterferon and ribavirin taken for 48 weeks and accompanied with numerous side effects and a 50% responsiveness to the treatment.

Harvoni is a ledipasvir-sofosbuvir combination that can be used for 12-24 weeks if available. The next choice is Vekira Pak for 12-24 week.

► Treatment of chronic hepatitis C genotypes 2 and 3 (non-1)

In 80% of the cases, treating hepatitis with peginterferon and ribavirin eradicates the virus. Other medications should be used in patients experiencing cirrhosis of the

liver and unable to use peginterferon or in patients with peginterferon resistance. The administration of harvoni for 12-24 weeks is also recommended.



► Alcohol and hepatitis C

It should be noted that not only does the use of alcohol cause liver damage, but it also interferes with the treatment of hepatitis C.

- How does alcohol damage the liver?

- Alcohol increases fat production in the liver, resulting in liver damage and cirrhosis.
- Alcohol interferes with the self-repairing capacity of the liver.
- The higher the consumption of alcohol, the higher the risk of liver damage.
- The kind of alcohol consumed has nothing to do with the occurrence of damage and all types of alcohol are equally harmful.

All kinds and amounts of alcohol damage the liver.

The concurrent effects of alcohol and hepatitis C on the liver double the risk of liver damage. The risk of cirrhosis (a lazy liver) and liver cancer is higher and more imminent in hepatitis C patients who also drink alcohol.

The blood levels of the virus determined through the quantitative measurement of HCV RNA are directly correlated with the amount of alcohol consumed. Alcohol presents greater risks for women.

If patients continue drinking alcohol, no medicine can be administered to control hepatitis C.



Can patients continue drinking alcohol in moderate amounts?

*No;
any amount of alcohol can indeed damage the liver. It should be noted that the use of alcohol increases the risk of acetaminophen toxicity.*

► Hepatitis C and diet

There are different opinions about the patients' suggested type of diet and the types of food they should eat or avoid. Nevertheless, the key point is to determine the severity of the liver disease and to avoid strict diets.

Liver has a key role in the body's metabolism, and if damaged, the body does not receive enough calories and the excretion of excess toxin produced from the metabolism of substances is no longer possible. In case of severe liver diseases, patients should avoid meat (especially red meat) and opt for white meat only, such as fish and poultry, and use vegetable proteins. Eating fresh vegetables and fruits full of antioxidants is also highly effective. Patients should avoid the consumption of smoked food

containing nitrates, such as sausages and cold cuts, and avoid chemical food additives, such as food coloring and condiments. In general, patients should avoid overindulgence in food and obesity (being overweight). The use of distilled chicory, licorice and silybum marianum water is useful for the liver. The daily consumption of two teaspoons of honey or 2 dates is also beneficial.

? Are patients with hepatitis C allowed to use pain relievers, such as acetaminophen or ibuprofen?

Before answering this question, the severity of the liver lesion should be determined. The majority of patients do not show an evident liver failure and are free to use pain relievers (if necessary and according to the physician's order). It should be noted that the majority of patients requiring treatments with interferon have to use pain relievers. Patients with chronic liver disease also have to be cautious when using certain antibiotics and sedatives.



► **Silybum marianum**

Silybum marianum or silymarin is a known medicinal herb beneficial in the treatment of liver diseases; its benefits for the liver have been known since 2000 years ago. Over 200 studies have been conducted to date in Europe (mainly Germany), South America and Japan on the therapeutic effects of this medication on chronic

hepatitis. The root and leaf extract this herb comes in the form of a milky white liquid. This medication is currently manufactured in the form of capsules and syrups and is used for preventing the exacerbation of liver lesions. The medication inhibits oxygen free radicals and prevents cell damage.

This medication has not presented any side effects and can be used by pregnant and breastfeeding women. The medication should be administered at 140-mg doses 2-3 times per day.

Silybum marianum is a known medicinal herb effective in the treatment of liver diseases.

Patients with hepatitis C should pay attention to the following key points:

- Patients should visit their physician for regular examinations and periodic specialized tests for determining their liver functioning.
- When visiting the dentist or the physician or going into a laboratory or any other place with the risk of transmission of the virus to others, the patient must inform everyone involved of his infection with hepatitis C virus.
- Alcohol exacerbate the disease. Patients should seriously avoid its consumption.
- Patients should avoid donating blood.
- Overweight patients should try to lose weight.
- Patients should not share their personal items, such as tooth brushes, razors, towels, etc.
- Patients with hepatitis C can live and exercise just as other people and do not have any dietary limitations unless they are overweight or have high blood fat and glucose levels.



- Patients with hepatitis C can marry just as well as others. The risk of transmission of the infection is very low in a healthy sex life.



A Comprehensive Guide For Hepatitis C

CHAPTER 11

Liver transplant

Although liver transplant has brought much hope to patients with cirrhosis suffering from its complications or patients with liver cancer, it is not accessible to all patients. It is estimated that about 5 thousand people die every year in Iran from liver diseases while many can survive if liver transplant becomes accessible to them. Many of these patients are currently in the waiting list for receiving a liver transplant. Organ donation under conditions of brain death has not yet become part of the national culture of the country. Nevertheless, the early diagnosis of hepatitis C and its successful treatment reduce the need for liver transplants.

Liver transplant is performed in patients with hepatitis C experiencing advanced liver damage and not responding to pharmacotherapy. Although the virus invades the transplanted liver in all the cases, the transplanted liver has very few liver lesions.

The first liver transplant was performed in 1963; at the beginning, the majority of patients survived only a few months and died from liver failure or other complications of the transplant. Nevertheless, physicians and patients did not give up until the condition of patients receiving liver transplants were improved around 1981 with the improvements in the quality of the transplants and the introduction of new effective medications.



- When is liver transplant recommended to patients?

The answer is not simple, but what is evident is that a liver transplant is not necessary during the primary stages of the disease. If the patients' liver conditions do not improve in spite of medical treatments and the disease progresses toward a lazy liver and puts the patient's life at risk, they are advised to receive a liver transplant.

Can the transplanted liver be infected with

- hepatitis C virus after the transplant?

Yes; hepatitis C relapses in almost all patients who have received a liver transplant. The liver disease will progress rapidly due to the immunosuppressant drugs used. Numerous studies are currently being conducted to determine the role of treatment with interferon or a two-drug therapy in patients with a liver transplant. Nevertheless, longevity and survival is acceptable in patients with hepatitis C after a liver transplant and there are no restrictions against receiving a liver transplant for these patients. In fact, over 90% of them enjoy an active life up to three years after the transplant. The introduction of new oral anti-hepatitis C virus medications has made

great improvements in patients with a liver transplant. Nevertheless, patients experience an excellent lifestyle after their liver transplant. They no longer suffer from yellowing and jaundice, itching, accumulation of a large amount of fluid in the abdomen and mental disorders and regain their reproductive ability.

After the transplant, the patient will require the long-term use of various medications to protect the transplanted liver.

One advantage of receiving a liver transplant is that it can be performed on patients with hepatocellular carcinoma. It should be noted, however, that liver transplant is an expensive procedure that is not accessible everywhere.

- What are your recommendations for after a liver transplant?

Patients are usually kept for several days in an intensive care unit after the surgery and then hospitalized for 4 weeks. During the hospitalization period, necessary examinations are performed for checking the transplanted liver conditions and for inspecting potential rejections. Periodical (monthly) blood tests and regular examinations are then performed after the patient's discharge from the hospital. Given that the medications used, such as Tacrolimus and cyclosporine can increase blood pressure, regular blood pressure monitoring is also necessary. The risk of liver transplant rejection is often more serious during the first weeks after the surgery.

Ref

1. Sharafi H, **Alavian SM**, Keshvari M. Efficacy of 24-week pegylated interferon alpha and ribavirin combination therapy in highly selected patients infected with hepatitis C virus genotype 1. *Hepat Mon.* 2015;15(1):e24955.
2. Sandoughdaran S, **Alavian SM**, Sharafi H, Behnava B, Salimi S, Mehrnough L, et al. Efficacy of Prolonged Treatment With Pegylated Interferon (Peg-IFN) and Ribavirin in Thalassemic Patients With Hepatitis C Who Relapsed After Previous Peg-IFN-Based Therapy. *Hepat Mon.* 2015;15(1):e23564.
3. Sharafi H, **Alavian SM**, Keshvari M. Alanine transaminase as a single marker is not reliable for selecting candidates of pegylated interferon and ribavirin treatment. *J Formos Med Assoc.* 2014.
4. Sargolzaee Aval F, Behnaz N, Raoufy MR, **Alavian SM**. Predicting the outcomes of combination therapy in patients with chronic hepatitis C using artificial neural network. *Hepat Mon.* 2014;14(6):e17028.
5. Sadeghi F, Bokharaei-Salim F, Salehi-Vaziri M, Monavari SH, **Alavian SM**, Salimi S, et al. Associations between human TRIM22 gene expression and the response to combination therapy with Peg-IFNalpha-2a and ribavirin in Iranian patients with chronic hepatitis C. *J Med Virol.* 2014.
6. Pourhoseingholi MA, Ashtari S, **Alavian SM**. Sofosbuvir vs. Combination of Pegylated Interferon and Ribavirin; How Much Shall Pay for Iranian Patients? *Hepat Mon.* 2014;14(11):e25540.
7. Bokharaei-Salim F, Keyvani H, Salehi-Vaziri M, Sadeghi F, Monavari SH, Mehrnough L, et al. Mutations in the NS5A gene of hepatitis C virus subtype 1b and response to peg-IFNalpha-2a/RBV combination

therapy in Azerbaijani patients. Arch Virol. 2014;159(11):2893-9.

8. **Alavian SM**. Determination of Whether Vitiligo is a Contraindication to Interferon Therapy in Chronic Hepatitis C. Journal of Skin & Stem Cell. 2014;1(1):e16639.

9. Abbasinazari M, **Alavian SM**, Behnava B, Asgharinia M, Salimi S, Keshvari M, et al. Effect of zinc supplementation on viral response in patients with chronic hepatitis C and Beta thalassemia major, a pilot study. Journal of clinical and diagnostic research : JCDR. 2014;8(12):HC16-9.

10. Zayeri F, Chaibakhsh S, Pourhoseingholi A, Akbarzadeh Baghban A, **Alavian SM**. Random effect model for identifying related factors to virological response in HCV patients. Gastroenterol Hepatol Bed Bench. 2013;6.

11. Mehrzmay A, **Alavian SM**, Moradi-Lakeh M, Mokhtari Payam M, Hashemi-Meshkini A, Behnava B, et al. Cost-Effectiveness Analysis of Adding Low Dose Ribavirin to Peginterferon Alfa-2a for Treatment of Chronic Hepatitis C Infected Thalassemia Major Patients in Iran. Hepat Mon. 2013;13(9):e10236.

12. Ebrahimi Daryani N, **Alavian SM**, Somi MH, Torabi-Nami M. Hepatitis C and Why the Treatment is Needed Now? The Summary Report From the Cross-Border Symposium of the 5th Tehran Hepatitis Congress May 2013. Hepat Mon. 2013;13(11):e16082.

13. **Alavian SM**. Sofosbuvir has come out of the magic box. Hepat Mon. 2013;13(12):e16916.

14. Vahedi M, Pourhoseingholi A, Ashtari S, Pourhoseingholi MA, Karkhane M, Moghimi-Dehkordi B, et al. Using statistical models to assess medical cost of hepatitis C virus. Gastroenterol Hepatol Bed Bench. 2012;5(Suppl1):S31-S6.

15.Tabatabaei SV, **Alavian SM**, Keshvari M, Behnava B, Miri SM, Karimi Elizee P, et al. Low dose ribavirin for treatment of hepatitis C virus infected thalassemia major patients; new indications for combination therapy. *Hepat Mon.* 2012;12(6):372-81.

16.Sharafi H, Pouryasin A, **Alavian SM**, Behnava B, Keshvari M, Mehrnoush L, et al. Development and Validation of a Simple, Rapid and Inexpensive PCR-RFLP Method for Genotyping of Common IL28B Polymorphisms: A Useful Pharmacogenetic Tool for Prediction of Hepatitis C Treatment Response. *Hepat Mon.* 2012;12(3):190-5.

17.Qureshi S, Shafiei-Guilani M, Aalaei-Andabili SH. Why is the sustained virological response rate among HCV genotype 3 infected patients in Pakistan low? *J Coll Physicians Surg Pak.* 2012;22(1):70-1; author reply 1.

18.Nejad MR, **Alavian SM**. Should routine screening for celiac disease be considered before starting interferon/ribavirin treatment in patients affected by chronic hepatitis C or not? *Bratisl Lek Listy.* 2012;113(4):251.

19.Namazee N, Sali S, Asadi S, Shafiei M, Behnava B, **Alavian SM**. Real response to therapy in chronic hepatitis C virus patients: a study from iran. *Hepat Mon.* 2012;12(9):e6151.

20.Motavaf M, Safari S, **Alavian SM**. Therapeutic potential of RNA interference: a new molecular approach to antiviral treatment for hepatitis C. *J Viral Hepat.* 2012;19(11):757-65.

21.Amini S, **Alavian SM**, Mostafavi E, Vahabpour R, Bahramali G, Aghasadeghi MR, et al. Presence of plus-strand HCV RNA in serum and PBMC as an indicator for relapse and resistance to IFN therapy in patients infected by HCV. *Future Virol.* 2012;7(3):1-8.

22.**Alavian SM**, Tabatabaei SV, Behnava B. Impact of erythropoietin

on sustained virological response to peginterferon and ribavirin therapy for HCV infection: a systematic review and meta-analysis. *J Viral Hepat.* 2012;19(2):88-93.

23. **Alavian SM**, Shafiei-Guilani M, Alaei SH. Why is the Sustained Virological Response Rate Among HCV Genotype 3 Infected Patients in Pakistan Low? *J Coll Phy Surg Pak.* 2012;22(1):69-72.

24. **Alavian SM**, Menati M, Shabani M, Shafiei M, Kolbadi Nejad M. Long-term outcomes of chronic hepatitis C patients treated with pegylated interferon 2a plus ribavirin in Iran. *African J of Micro Res.* 2012;6(20):4298-301.

25. **Alavian SM**, Lankarani KB, Sharara A. Treatment of Chronic HCV in Special Populations: Thalassemia, Hemophilia, and Hemodialysis Patients. *Curr Hepat Rep.* 2012;11(4):256-62.

26. **Alavian SM**, Jabbari H, Daryani NE, Torabi Nami M. Hepatitis C Virus: The Rising Concerns and Growing Hopes, Report From the HCV Symposium, Fourth Tehran Hepatitis Congress, november 2011, Tehran, Iran. *Hepat Mon.* 2012;12(7):423-9.

27. **Alavian SM**, Aalaei-Andabili SH. Education by a nurse increases the adherence to therapy in chronic hepatitis C patients. *Clin Gastroenterol Hepatol.* 2012;10(2):203; author reply

28. Alavi Moghaddam M, Zali MR, Aalaei Andabili SH, Derakhshan F, Miri SM, **Alavian SM**. High Rate of Virological Response to Peginterferon alpha-2a-Ribavirin Among Non-Cirrhotic Iranian Hemophilia Patients With Chronic Hepatitis C. *Iran Red Crescent Med J.* 2012;14(8):466-9.

29. Sharafi H, **Alavian SM**. IL28B polymorphism, Explanation for Different Responses to Therapy in Hepatitis C Patients. *Hepat Mon.* 2011;11(12):958-9.

30. Bokharaei-Salim F, Keyvani H, Monavari SH, **Alavian SM**, Madjd Z, Toosi MN, et al. Occult hepatitis C virus infection in Iranian patients with cryptogenic liver disease. *J Med Virol*. 2011;83(6):989-95.

31. Behnava B, Keshvari M, Miri SM, Karimi Elizee P, **Alavian SM**. Reactivation of Brucellosis during Pegylated Interferon-alpha therapy in a Thalassaemic patient with Chronic Hepatitis C. *E&C Hepatology*. 2011;7(1-2):57-9.

32. **Alavian SM**, Tabatabaei SV, Behnava B, Mahboobi N. Optimal duration of treatment for HCV genotype 1 infection in slow responders: a meta-analysis. *Hepat Mon*. 2011;11(8):612-9.

33. **Alavian SM**, Lankarani KB, Aalaei-Andabili SH, Pouryasyn A, Ebrahimi Daryani N, Nassiri Toosi M, et al. Treatment of Chronic Hepatitis C Infection: Update of the Recommendations from Scientific Leader's Meeting-28th July 2011-Tehran, IR Iran. *Hepat Mon*. 2011;11(9):703-13.

34. **Alavian SM**. Commentary on: Treatment of HCV infection in chronic kidney disease. *Nefrologia*. 2011;31(5):607.

35. **Alavian SM**. Herbal medicine and liver disease, for any conclusion we need to do more studies. *J Res Med Sci*. 2011;16(7):974-5.

36. **Alavian SM**, Tabatabaei SV, Keshvari M, Behnava B, Miri SM, Elizee PK, et al. Peginterferon alpha-2a and ribavirin treatment of patients with haemophilia and hepatitis C virus infection: a single-centre study of 367 cases. *Liver Int*. 2010;30(8):1173-80.

37. **Alavian SM**, Tabatabaei SV. Meta-analysis of factors associated with sustained viral response in patients on hemodialysis treated with standard or pegylated interferon for hepatitis C infection. *Iran J Kidney Dis*. 2010;4(3):181-94.

A COMPERHENSIVE GUIDE FOR HEPATITIS C

38. **Alavian SM**, Behnavab B, Tabatabaei SV. The comparative efficacy and safety of peginterferon alpha-2a vs. 2b for the treatment of chronic HCV infection: a meta-analysis. *Hepat Mon.* 2010;10(2):121-31.

39. **Alavian SM**, Behnavab B, Tabatabaei SV. Comparative efficacy and overall safety of different doses of consensus interferon for treatment of chronic HCV infection: a systematic review and meta-analysis. *Eur J Clin Pharmacol.* 2010;66(11):1071-9.

40. **Alavian SM**, Behnavab B, Tabatabaei SV. Erythropoietin adjuvant therapy and sustained virological response in HCV-infected patients. *Aliment Pharmacol Ther.* 2010;32(3):509-10.

41. **Alavian SM**. Acute psychosis after therapy with Peginterferon alpha 2a (Pegaferon) in chronic Hepatitis C. *Pak J Med Sci.* 2010;26(4):985-6.

42. Ziaee A, Esfahanian F, **Alavian SM**, Sarreshtedari M. Thyroid Dysfunction in Patients with Chronic Viral Hepatitis B and C during Alpha Interferon Therapy. *Hepat Mon.* 2009;9(2):110-3.

43. Hosseini Moghaddam SM, **Alavian SM**, Rahnavardi M. Therapeutic aspects of hepatitis C in hemodialysis patients. *Am J Nephrol.* 2009;29(2):123-8.

44. **Alavian SM**, Tabatabaei SV, Ayyub M. Outcome of combination antiviral therapy in hepatitis C virus infected patients with sickle cell disease. *Saudi Med J.* 2009;30(8):1107-8.

45. **Alavian SM**, Tabatabaei SV. Conventional Interferon Alpha Therapy of Chronic Hepatitis C in Patients with End Stage Renal Disease, Six versus Twelve Months? A Meta-Analysis. *Nephrourol Mon.* 2009;1(1):4-13.

46. **Alavian SM**, Abolghasemi H, Miri SM, Keshvari M, Karimi Elizee

P, Behnava B, et al. Safety and Efficacy of Pegylated Interferon Alfa-2a for the Treatment of Hepatitis C in Patients with Major Thalassemia. *IJBC*. 2009;1(4):129-37.

47. **Alavian SM**. Therapy of Hepatitis C in Hemodialysis Patients with Pegylated Interferon/Need more Studies for a Conclusion. *Prilozi*. 2009;30(1):243.

48. **Alavian SM**, Kabir A, B H, Nayeypour M, Doroudi T, Baralle F. Preliminary Report of Interferon α 2b in Combination with Ribavirin for 48 Weeks for Treatment of Iranian Patients with Chronic Hepatitis C: A Quasi-Experimental Study. *Shiraz E-Med J*. 2006;7(1).

49. **Alavian SM**, Foroutan H, Mirmomen S, Ghofrani H, Kabir A. Efficacy and safty of combination therapy of interferon-alfa 2b plus ribavirin for chronic hepatitis C. *Med J Islam Repub Iran*. 2006;19(4):291-5.

50. **Alavian SM**. Are the Real HCV Infection Features in Iranian Patients the Same As What Is Expected? *Hepat Mon*. 2005;5(1):3-5.

51. Zokaee A, Mirmomen SS, Ebrahimi-Daryani N, Haghpanah B, Poorsamimi P, **Alavian SM**, et al. A comparative study between pegylated versus conventional interferon for the treatment of chronic hepatitis C infection in adult transfusion dependent thalassemic patients: an open label, randomized trial. *Gut*. 2004;36(1):A 169.

52. Mirmomen S, Ebrahimi DN, Malekzadeh R, Zali MR, **Alavian SM**, Haghpanah B, et al. The Efficacy and Safety of Peginterferon Alpha-2a (PEGASYS) Monotherapy in the Treatment of Chronic Hepatitis C infected Subjects with Transfusion Dependent Thalassemia. *Hepat Mon*. 2004;4(7):65-70.

53. Mirmomen S, Ebrahimi Daryani N, Malekzadeh R, **Alavian SM**, Haghpanah B, Poorsamimi A, et al. Efficacy and safety of PEGASYS monotherapy in the tretament of chronic hepatitis C infected subjects

with transfusion dependent thalassemia. *J Gastroenterol Hepatol*. 2004;19(suppl):A861.

54. **Alavian SM**, Mirmomen S, Bagheri-Lankarani K, Adibi P, Merat SH. Management of hepatitis C infection (regional guideline). *Hepat Mon*. 2004;4:2-19.

55. **Alavian SM**, Kabir A, Hajibaygi B, Dourodi T, Saber HR. [Efficacy of PDferon-B plus ribavirin in chronic hepatitis C: Quasi-experimental study]. *Physiology and Pharmacology*. 2004;8(1):71-81.

56. **Alavian SM**, Hajarizadeh B, Hajibaygi B, Doroudi T, Hamadanizadeh AK, Abar K. Efficacy and Safety of Pegylated interferon Alfa-2a plus Ribavirin for treatment of chronic hepatitis C and cirrhosis in Iran. *Hepat Mon*. 2004;4(7):53-8.

57. **Alavian SM**, Hajarizadeh B. Attempted Suicide in Two Patients With Chronic Hepatitis C While Being Treated With Interferon-alpha. *Hepat Mon*. 2004;4(6):20-2.

58. **Alavian SM**, Doroudi T. Interferon α -2a in chronic hepatitis C infection in hemophiliac patients. *Shiraz E-Med J*. 2004;5(1):1-6.

59. **Alavian SM**, Kabir A, Hashemi A. Evaluation of interferone-Alpha type 2a (ROFERON) on patients with chronic hepatitis C. *J Iran Univ Med Sci*. 2003;10(33):61-74.

60. **Alavian SM**, Doroudi T, Hajarizadeh B, Hajibighi B. Interferon therapy in hemophiliac patients with chronic hepatitis C. *Transfusion Today*. 2002;52:4.

61. Younossi ZM, Park H, Saab S, Ahmed A, Dieterich D, Gordon SC. Cost-effectiveness of all-oral ledipasvir/sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection. *Aliment Pharmacol Ther*. 2015;41(6):544-63.

62. Turker K, Tas B, Ozkaya M, Tas E, Caglar A, Tetikkurt US. Dys-trophic-Anagen Effluvium Occurring During Pegylated Interferon-alpha-2a/Ribavirin Therapy. *Hepat Mon.* 2015;15(3):e24804.
63. Komur S, Kurtaran B, Inal AS, Pullukcu H, Ulu A, Kuscu F, et al. Telaprevir experience from Turkey. *Hepat Mon.* 2015;15(2):e25639.
64. Jafari A, Khalili H, Izadpanah M, Dashti-Khavidaki S. Safely treating hepatitis C in patients with HIV or hepatitis B virus coinfection. *Expert Opin Drug Saf.* 2015:1-19.
65. Chen SH, Peng CY, Lai HC, Su WP, Lin CH, Li YF, et al. An index to predict ribavirin-induced anemia in asian patients with chronic genotype 1 hepatitis C. *Hepat Mon.* 2015;15(3):e27148.
66. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, et al. Retreatment of HCV with ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin. *N Engl J Med.* 2014.
67. Younossi ZM, Stepanova M, Nader F, Jacobson IM, Gane E, Nelson D, et al. Patient-reported outcomes in chronic hepatitis C patients with cirrhosis treated with sofosbuvir-containing regimens. *Hepatology.* 2014.
68. Watts G. Hepatitis C could be virtually eliminated by 2030, experts believe. *BMJ.* 2014;348:g2700.
69. Traynor K. Sofosbuvir approved for chronic hepatitis C infection. *Am J Health Syst Pharm.* 2014;71(2):90.
70. Singal AG, Pillai A, Tiro J. Early Detection, Curative Treatment, and Survival Rates for Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis: A Meta-analysis. *PLoS Med.* 2014;11(4):e1001624.
71. Sikorska K, Romanowski T, Stalke P, Izycka Swieszewska E,

A COMPERHENSIVE GUIDE FOR HEPATITIS C

Bielawski KP. Association of hepcidin mRNA expression with hepatocyte iron accumulation and effects of antiviral therapy in chronic hepatitis C infection. *Hepat Mon.* 2014;14(11):e21184.

72. Shiffman ML, Benhamou Y. HCV F1/F2 patients: treat now or continue to wait. *Liver Int.* 2014;34 Suppl 1:79-84.

73. Shavakhi A, Minakari M, Bighamian A, Sadeghian S, Shavakhi S, Khamisi N, et al. Statin efficacy in the treatment of hepatitis C genotype I. *J Res Med Sci.* 2014;19(Suppl 1):S1-4.

74. Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. *Liver Int.* 2014;34 Suppl 1:69-78.

75. Sarvari J, Norozian H, Fattahi MR, Pirbonyeh N, Moattari A. The Role of Interferon Gamma Gene Polymorphism (+874A/T, +2109A/G, and -183G/T) in Response to Treatment Among Hepatitis C Infected Patients in Fars Province, Southern Iran. *Hepat Mon.* 2014;14(1):e14476.

76. Saiz de la Hoya P, Portilla J, Marco A, Garcia-Guerrero J, Faraco I, Anton J, et al. Directly observed therapy for chronic hepatitis C: A randomized clinical trial in the prison setting. *Gastroenterol Hepatol.* 2014.

77. Rezaee-Zavareh MS, Einollahi B. Treatment of occult hepatitis C virus infection: does it need special attention? *Hepat Mon.* 2014;14(7):e16665.

78. Reddy KR, Wirjosemito A, Pavri TM, Sinese L. HCV Therapy With Daclatasvir, PEG-IFN, and RBV After Boceprevir-Based Therapy Failure Post-Liver Transplantation in Hyper-IgM Syndrome. *Transplantation.* 2014;97(8):e47-8.

79. Ravi S, Nasiri-Toosi M, Karimzadeh I, Khalili H, Ahadi-Barzoki M, Dashti-Khavidaki S. Pattern and associated factors of anti-hepatitis C

virus treatment-induced adverse reactions. *Expert Opin Drug Saf.* 2014.

80. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. *N Engl J Med.* 2014.

81. Pol S, Vallet-Pichard A, Corouge M. Treatment of hepatitis C virus genotype 3-infection. *Liver Int.* 2014;34 Suppl 1:18-23.

82. Paterson JC, Miller MH, Dillon JF. Update on the treatment of hepatitis C genotypes 2-6. *Curr Opin Infect Dis.* 2014;27(6):540-4.

83. Miller MH, Agarwal K, Austin A, Brown A, Barclay ST, Dundas P, et al. Review article: 2014 UK consensus guidelines - hepatitis C management and direct-acting anti-viral therapy. *Aliment Pharmacol Ther.* 2014.

84. Mi Y, Gao YT, Jiao XL, Guo H, Liu T, Jing L, et al. The role of interleukin-28b gene polymorphisms in chinese patients with chronic hepatitis C treated with pegylated interferon and ribavirin. *Hepat Mon.* 2014;14(8):e18793.

85. Manns MP, Vierling JM, Bacon BR, Bruno S, Shibolet O, Baruch Y, et al. The Combination of MK-5172, Peginterferon, and Ribavirin is Effective in Treatment-Naive Patients with Hepatitis C Virus Genotype 1 Infection Without Cirrhosis. *Gastroenterology.* 2014.

86. Manns M, Marcellin P, Poordad F, de Araujo ES, Buti M, Horsmans Y, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2014.

87. Malaguarnera G, Pennisi M, Gagliano C, Vacante M, Malaguarnera M, Salomone S, et al. Acetyl-L-Carnitine Supplementation During

A COMPERHENSIVE GUIDE FOR HEPATITIS C

HCV Therapy With Pegylated Interferon-alpha 2b Plus Ribavirin: Effect on Work Performance; A Randomized Clinical Trial. *Hepat Mon.* 2014;14(5):e11608.

88. Leber A, Feld JJ. Does Eltrombopag Really ENABLE SVR? *Gastroenterology.* 2014;146(2):339-42.

89. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. *N Engl J Med.* 2014.

90. Koff RS. Review article: the efficacy and safety of sofosbuvir, a novel, oral nucleotide NS5B polymerase inhibitor, in the treatment of chronic hepatitis C virus infection. *Aliment Pharmacol Ther.* 2014.

91. Khorrami S, Mohammadpour H, Shahzamani K, Zarif MN, Sharifi AH, Merat S, et al. The relationship between HLA-G and viral loads in non-responder HCV-infected patients after combined therapy with IFN-alpha2alpha and ribavirin. *Hum Immunol.* 2014.

92. Julicher P, Dhein J. The Range of Uncertainty: a Tool for Efficiently Addressing Result Variability Around Clinical Decision Points for Hepatitis C Response-guided Therapy. *Biomark Insights.* 2014;9:9-13.

93. Jayasekera CR, Barry M, Roberts LR, Nguyen MH. Treating Hepatitis C in Lower-Income Countries. *N Engl J Med.* 2014.

94. Jancoriene L, Norvydaite D, Galgauskas S, Balciunaite E. Transient visual loss in a hepatitis C patient treated with pegylated interferon alpha-2a and ribavirin. *Hepat Mon.* 2014;14(2):e15124.

95. Hoofnagle JH, Sherker AH. Therapy for hepatitis C--the costs of success. *N Engl J Med.* 2014;370(16):1552-3.

96. Heidari Z, Shahzamani K, Ghanbari R, Tahamsebifar A. Associa-

tion of SNPs in Interferon Receptor Genes in Chronic Hepatitis C with Response to Combined Therapy of Interferon and Ribavirin. *Acta Med Iran.* 2014;52(10):740-7.

97.Sanford M. Simeprevir: A Review of Its Use in Patients with Chronic Hepatitis C Virus Infection. *Drugs.* 2015.

98.Zhang H, Chao J, Zhu L, Song L, Li X, Liu P. Direct Economic Burden and Influencing Factors in Patients With Hepatitis B Virus Related Diseases in Jiangsu, China. *Asia Pac J Public Health.* 2014.

99.Wei L, Lok AS. Impact of new hepatitis C treatments in different regions of the world. *Gastroenterology.* 2014;146(5):1145-50 e1-4.