



European Liver Patients Association

Hepatitis C

Understanding a silent killer

**Facts, figures & background media information
about viral hepatitis C**





Tatjana Reic
President of ELPA

Introduction

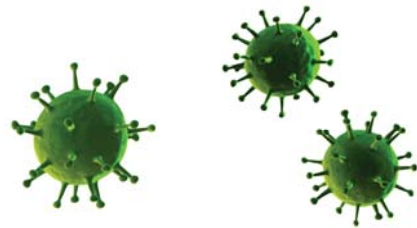
Up to 200 million people around the world suffer from hepatitis C. In Europe there are at least 9 million people who are infected with the virus. This is particularly serious as it is estimated that 90% of those infected by hepatitis C are not aware of their infection, as hepatitis C generally only causes serious symptoms in its final stages. There is also the fact that there is very little public awareness of this disease. Ignorance, excessive anxieties and prejudices also serve to ensure that hepatitis C is still a stigmatised disease.

A medical cure is possible for more patients today than in the past. However, treatments are often associated with severe side-effects, are not suitable for all patients nor are they equally available in all countries.

This booklet gives you an overview of hepatitis C: from the course of the disease via prevention from infection, current therapy options through to the epidemiological situation and the political dimensions of the disease.

Tatjana Reic
September 2012

Hepatitis C: Fast Facts



What is hepatitis C?

“Hepatitis” means an inflammation of the liver. An infection with the hepatitis C pathogen is a possible cause.

Learn more about the hepatitis C virus on Page 4

How can you protect yourself?

The virus is almost exclusively transmitted through contact with infected blood (blood-to-blood transmission). Simple codes of conduct can prevent infection. There is no vaccine protection.

Learn more about transmission paths and protection from infection on Page 5

What makes hepatitis C dangerous?

There is a risk of secondary diseases such as cirrhosis of the liver and liver cancer with every chronic liver infection. It is the same with hepatitis C.

Learn more about the progress of chronic hepatitis C on Page 7

The liver – what functions does it actually have?

The liver is involved in many vital processes in the body. If it is damaged, this can cause complications. If it fails, the patient’s life is threatened.

Learn more about the “unknown organ”: the liver on Page 8

Does hepatitis C not have any symptoms?

For very many patients chronic hepatitis C progresses without causing any specific symptoms. This means that it is often only detected after several years or decades.

Learn more about the symptoms of hepatitis C on Page 9

Who should get tested?

Some groups of people are at risk. Anyone who belongs to such a group should have him/herself

tested. People who received blood products before 1990 are also included, as are medical staff and intravenous drug users.

Learn more about groups with an increased risk of infection on Page 10

How is hepatitis C detected by the doctor?

If both antibodies against the virus and the virus's genotype are detected in the blood, then the patient has hepatitis C. If this continues for more than half a year, then the hepatitis C has become chronic.

Learn more about the diagnostic processes on Page 10

Can hepatitis C be cured?

Hepatitis C is curable. The treatment options for chronic hepatitis C are continually being improved and a cure will be possible for more patients in the future.

- Find a summary of treatment procedures on Page 12
- Side-effects are numerous. Find out more on Page 14
- Learn more about future and alternative treatments on Page 17

And if the treatment doesn't work?

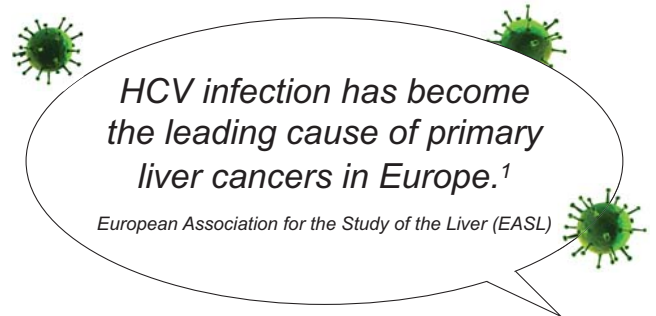
The treatment is not equally effective for all patients. A second treatment is possible in principle, but this may also not lead to a cure for all patients.

Learn more about treatment failure on Page 15

Liver transplant. A possible solution?

A transplant cannot provide a cure. It is only possible to prevent an infection of the donor organ under certain conditions and this is only rarely possible in practice.

Learn more about hepatitis C and liver transplantation on Page 19



Stigma.

Hepatitis C is not just a disease associated with marginal groups and drug users. Many patients suffer from prejudice and stigmatisation. The media also contributes to this indirectly.

Learn more about this great hurdle for many sufferers on Page 20

Hepatitis C in Europe and the rest of the world.

Up to 200 million people are infected with hepatitis C. Many die from its consequences. Hepatitis C is the main cause of liver cancer today.

Learn more about the current situation on Page 23

The political dimension of hepatitis C.

The WHO has called for greater prevention. Self-help organisations, such as the ELPA, work on behalf of sufferers, for a better social and political response, and simply for more action.

Learn more about prevention strategies and self-help in Europe on Page 24

European Liver Patients Association

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1. What is hepatitis?

“Hepatitis” – is an umbrella term for liver inflammations due to the most varied causes.

Hepatitis C is an inflammation of the liver caused by a viral infection. “Hepatitis” is a general term for an “inflammation of the liver” and should be understood completely independently from the causative agent. Hepatitis can be caused by certain viruses (hepatitis A, B, C, D or E) – but also by metabolic diseases, such as e.g. steatohepatitis or certain autoimmune diseases (autoimmune hepatitis). A liver inflammation is also possible due to harmful environmental influences (alcohol, toxins, etc.). This means that not every case of hepatitis is infectious.

Viral hepatitis A, B and C

Viral hepatitis is an infectious form of hepatitis. Different viruses, which can cause hepatitis, must be considered. Even although they all cause an inflammation of the liver, the viruses are still very different from one another. The transmission paths, progress of the disease and the severity of the disease and its treatment are all quite different.

While hepatitis A and E are generally cured spontaneously by the immune system, hepatitis C becomes chronic in most infected people (up to 80%). On the other hand, it is exactly the opposite case with hepatitis B: in adults, approximately 10% of infected patients have to reckon with hepatitis B becoming chronic. Vaccines have as yet only been established for hepatitis A and B.²

The designation of viral types – i.e. hepatitis A, B, C, etc. describes the different viruses and has nothing to do with the severity of the disease. Also, the viruses cannot change into one another. The hepatitis viruses A and B were discovered in the 1960s and 70s; while hepatitis C was first identified as a separate virus in 1989.

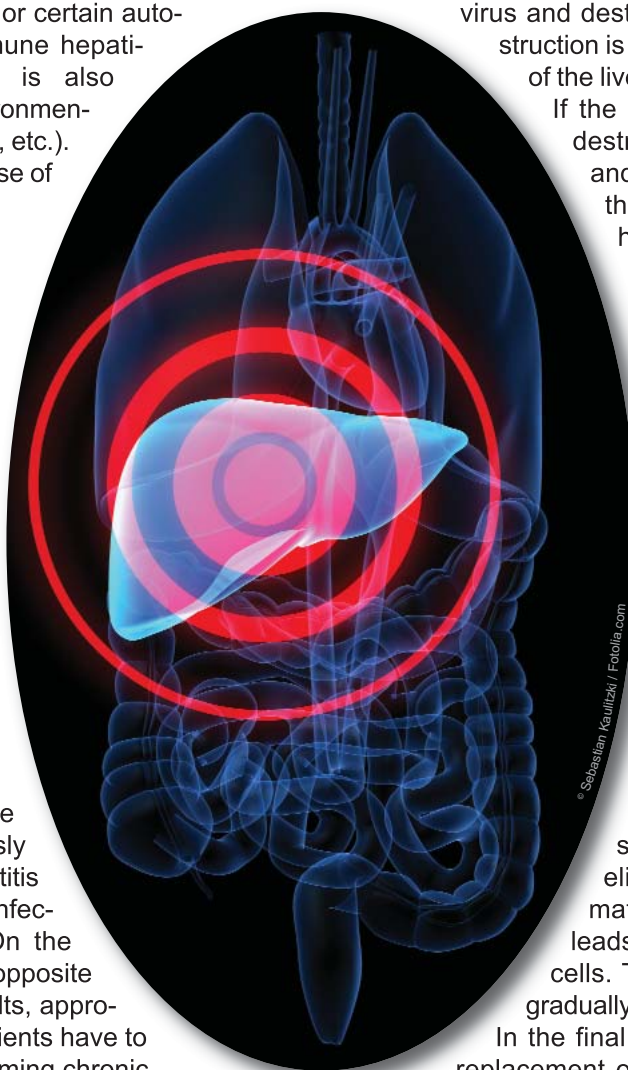
What does the hepatitis C virus actually do in the body?

Put simply, the process can be described as follows: when the hepatitis C virus enters a person’s bloodstream, it “seeks out” the way to the liver and penetrates the liver cells. Once there, it begins to reproduce. The virus itself uses the liver cell to multiply, but does not harm it directly. The immune system then detects the cells infected with the virus and destroys them. This action of destruction is expressed as an inflammation of the liver. This is an acute hepatitis C.

If the immune system succeeds in destroying all the infected cells, and thus also the virus, one can then speak of a spontaneous healing. In this way, approximately 20–50% of infected people manage to overcome acute hepatitis C. Antibodies against the virus also remain behind after the infection has come to an end.

However, in most patients (up to 80%) hepatitis C becomes chronic. The infection is chronic, if it remains in the body for longer than six months and the HCV-RNA in the blood is still positive. In cases of chronic hepatitis C the immune system has not managed to detect and eliminate all the infected cells completely. Instead of the virus being eliminated it causes an inflammation of the liver, which also leads to the destruction of healthy cells. The long-lasting inflammation gradually leads to a scarring of the liver. In the final stages it causes a complete replacement of liver tissue, which is called cirrhosis.

Once hepatitis C has become chronic, a medical treatment is the only possible cure. However, as the processes described largely go unnoticed by the majority of patients, it can often take years or decades until the hepatitis C is diagnosed. This is also part of what makes chronic hepatitis C so “threatening”. The acute phase often progresses without any symptoms, or only non-specific symptoms occur. The chronic phase is also rarely accompanied by any definite symptoms.³ As it goes unnoticed by the sufferer him/herself, it can lead to



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liver damage. Diagnosis often only happens late and by chance. By this point in time, complications, such as fibrosis or cirrhosis of the liver, may have already occurred. This is first of all a shock to many patients. Incidentally, not every contact with the hepatitis C virus leads automatically to an infection. Whether the virus can actually settle in the liver, also depends on the quantity of the virus transmitted. Not every bodily fluid is equally infectious and not every transmission path is equally risky. For hepatitis C, blood-to-blood transmission poses by far the highest risk. Any contact with infected blood should be avoided.

“Blood-to-blood” transmission

For an infection with hepatitis C infected blood (or the virus contained in it) must enter the bloodstream of another person. Such a “blood-to-blood” transmission is possible e.g. from unclean needles and medical instruments; until 1990 the virus was also frequently transmitted by blood transfusions and/or other blood products.

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2. Transmission and protection from infection

Transmission paths

Hepatitis C is transmitted almost exclusively through blood-to-blood contact. If infected blood enters the bloodstream of another person, this can cause a hepatitis C infection. Hepatitis C can be transmitted by:



a) Blood and blood products

It is only since 1991 that systematic checking of blood donors and blood products has been carried out for the hepatitis C virus, which had been identified only shortly before this time. Before 1991 the hepatitis C virus was transmitted many times via contaminated blood transfusions and other products made from blood or blood plasma, such as coagulants (e.g. for haemophilia patients/haemophiliacs) or immunoglobulins (e.g. anti-D immunoprophylaxis for rhesus-negative pregnant women). Blood transfusions and blood products in Europe are considered to be safe today



b) Shared use of drug paraphernalia and needles

The hepatitis C virus is frequently transmitted by the shared use of needles in intravenous drug use. Even sharing an aspiration tube (drug taking through the nose, or “snorting”) can lead to an infection with hepatitis C.



c) Contact with infected blood (e.g. needle-stick injuries)

In particular, people who work in the medical profession and thus also come into contact with blood, are at higher risk of becoming infected with the hepatitis C virus than people from other occupational groups. Accidental needle-stick injuries with contaminated needles and cannulae belong to the most frequent transmission paths in this instance.

d) Medical or surgical procedures

A transmission during operations or other medical and dental interventions is possible, if e.g. contaminated instruments are not sterilised or insufficiently sterilised. In this instance, the risk is likewise estimated to be low in Europe today.⁴



e) Use of unsterilised instruments in tattooing, piercing, acupuncture

The hepatitis C virus can be transmitted by using unclean instruments in tattooing or by dyes which are used more than once; when carrying out piercings or even reusing contaminated acupuncture needles.

Transmission is rarer through:

a) Sex

Sexual transmission of the hepatitis C virus is possible, but clearly much more unlikely than with hepatitis B. Hepatitis C is only rarely transmitted in monogamous heterosexual relationships. The risk of transmitting the virus increases, however, with more “hard core” sexual practices, which can cause damage to the mucous membrane, with anal intercourse or sex during menstruation. A condom should also certainly be used if there are any wounds in the genital area or other concomitant infections (e.g. herpes and HIV). Condoms are also recommended if there is a frequent change of sexual partners.

b) Pregnancy and birth

The risk of the hepatitis C virus being transmitted to the foetus or new-born baby from an infected mother before or during delivery is estimated to be around 1–6%.⁵ The risk of transmission cannot be reduced by a Caesarean section. Transmission of the virus is more frequent for expectant mothers, who are infected with both the hepatitis C virus and with HIV.

Experts generally do not advise against breastfeeding, as hepatitis C transmission is categorised as being highly unlikely. As a precautionary measure, however, they advise against it if nipples are inflamed and/or bleeding.

Hepatitis C cannot be contracted from:



- Hugging, cuddling, kissing
- Shaking hands
- Coughing, sneezing
- Shared use of toilets and bathrooms
- Shared use of swimming pools and saunas
- Eating from the same plate, with the same cutlery, drinking out of the same glass
- Food, which has been prepared by someone infected with hepatitis C
- Having a child on your lap or in your arms
- Clothing

The virus is hardly ever transmitted in everyday cohabitation and contact with a person infected with hepatitis C. There is no reason to avoid someone with hepatitis C for fear of infection or to behave differently towards them. It is only contact with his/her blood which must be avoided.

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How can you protect yourself from infection?

Hepatitis C is transmitted by infected blood. All protective measures are directed towards preventing contact with blood.

- Sharp and pointed personal hygiene objects should not be used jointly.
- Do not share nail scissors, nail clippers, razors.
- Do not share toothbrushes.
- Take care when treating bleeding wounds. Wear protective gloves.

Note: *It is not enough to cause an infection if blood flows over undamaged skin. It is only if the barrier of the skin is penetrated, e.g. if there is a small wound, that an infection with the hepatitis C virus is possible. Also by way of protection from other transmittable diseases, you should avoid any direct contact with blood in general.*



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- Drug users should only ever use their own needles and other drug paraphernalia.
- Condoms should be used by those who frequently change sexual partners, by homosexually active men and for “hard core” sexual practices, and intercourse during menstruation.⁶

Recommendations

- Laundry or crockery can be washed or rinsed as normal. Boiling is not necessary.
- Care should also be taken with dried blood: the virus can survive outside the body for several days depending on the environment, and even longer under certain conditions. How long the virus remains infectious during this time is not absolutely clear. The use of an antiseptic disinfection agent or an alcohol solution, such as e.g. 1-propanol is recommended.⁷

There is no vaccine against hepatitis C

Protection from infection with hepatitis C with a vaccine is unfortunately not possible. As yet, a protective vaccine is only possible against viral hepatitis A and B.

The hepatitis A and B vaccine is also recommended for hepatitis C patients, as an additional infection with these viruses could make the progress of the disease considerably worse.

Take-home messages:

- “Hepatitis” = liver inflammation. There are multiple possible causes, including hepatitis viruses
- Hepatitis C: a generally chronic inflammation of the liver – caused by an infection with the hepatitis C virus
- Progress is generally free of symptoms; despite an advanced degree of damage to the liver
- Main transmission path: contact with infected blood (blood-to-blood transmission).
- Objects, which could come into contact with blood, should not be used jointly with anyone else. (toothbrushes, nail scissors, razors, needles, ...)
- There is almost no danger of infection in everyday life
- Protection from hepatitis C through vaccination is not possible.

3. Progress of the disease

How does the disease express itself? What consequences can an infection with hepatitis C have for the liver?

Stage 1 – Acute hepatitis: The period of the first 6 months after infection is called an acute hepatitis C. During this time the immune system battles intensively with the virus. In 20-50% of cases this can lead to a spontaneous healing. After an infection, the incubation period lasts between 6 and 9 weeks. After this time the first symptoms may become noticeable (e.g. exhaustion, mild nausea, occasionally also a yellowing of the skin and eyes) – however, this is not inevitable. Hepatitis C can also progress without any symptoms. If the acute infection is detected promptly and treated with peginterferon the chances of recovery are very good at c. 90%.⁸

Stage 2 – Chronic hepatitis: For 50–80% of patients the immune system alone cannot eliminate the virus within six months. The liver inflammation then becomes chronic.

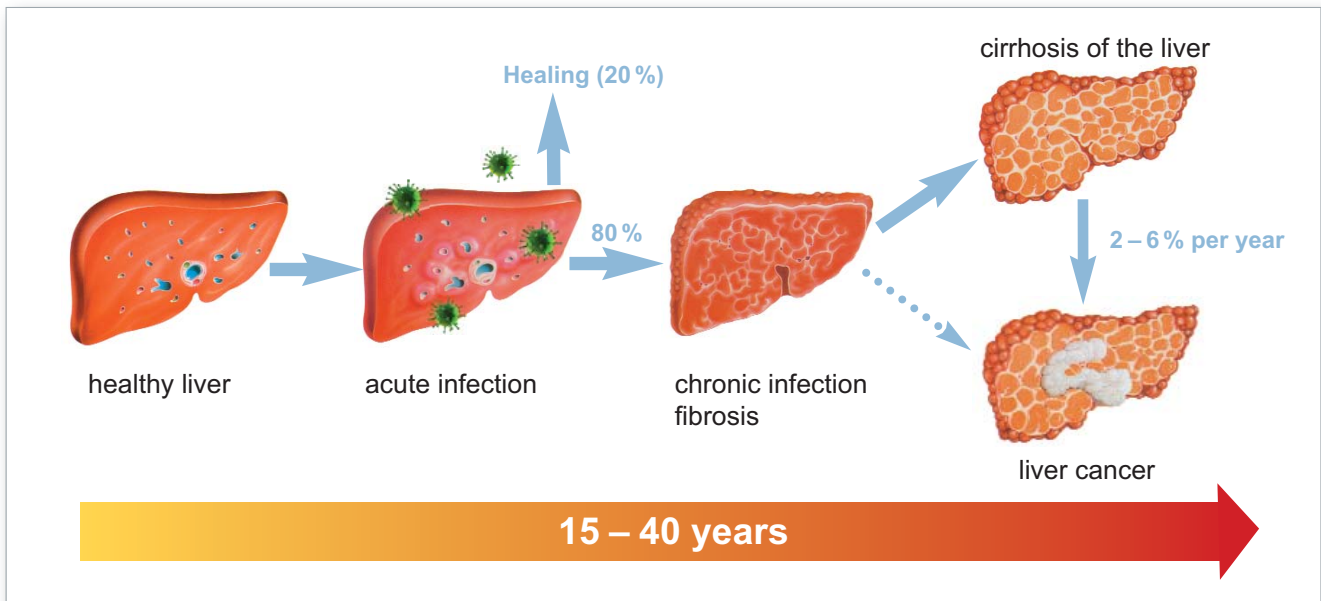
Stage 3 – Fibrosis: Untreated chronic hepatitis C can lead to a scarring of the liver over years or decades. While initially the destroyed liver cells can still be replaced by new liver cells, later in the course of the disease the gaps created are closed up by connective tissue cells, which have no function (scar tissue). This increasing scarring of the liver is called fibrosis. Fibrosis is a precursor stage of cirrhosis.

Stage 4 – Cirrhosis of the liver: When the scarring is so far advanced that it causes structural changes with nodular alterations, one speaks of cirrhosis of the liver.

At first, the liver can continue its functions despite the scarring for a long time and can compensate for the damage (“compensated cirrhosis”). Later, however, the liver becomes restricted in its functions (“decompensated cirrhosis”).

Complications, even including liver cancer and liver failure, become a threat.

- Abdominal dropsy (ascites)
- Haemorrhaging from varicose veins in the stomach or oesophagus (fundal or oesophageal varice bleeding)



- Brain disorders, confusion, even including coma (hepatic encephalopathies)
- Liver failure

With untreated hepatitis C, up to 40 % of patients develop cirrhosis.⁹ In general, this process from infection to cirrhosis takes about 30 years with hepatitis C.

Stage 5: Liver cancer: Liver cancer is a possible consequence of chronic liver diseases and mostly occurs in hepatitis C patients due to the liver becoming cirrhotic. Liver cancer is one of the most difficult types of cancer to treat and on the whole it does not have a good prognosis. The likelihood of dying within the first year of the diagnosis is 33%.¹⁰ A cure with an operation, radiofrequency ablation or transplantation is still today unfortunately only possible in a minority of patients. Other procedures, such as e.g. chemoembolization or using medication, such as sorafenib, may prolong survival, but will not heal the tumour disease fully.

Important note

- The course of the disease is often independent of the symptoms which the infection can cause! A chronic hepatitis C infection may progress more or less quickly no matter whether there are symptoms present or not.
- The quantity of the virus (HCV-RNA), which is detectable in the blood, has no impact on the progress of chronic hepatitis C! The liver damage can also progress more or less quickly, no matter how high or low the quantity of the virus.¹¹

Exception: Patients who have had a liver transplant often make poorer progress with a high quantity of the hepatitis C virus.¹²

The liver: What function does it have in the body?

No organ in our body has so many functions as the liver. No life is possible without the liver. It is involved in all the body's vital processes. From the conversion and preparation of nutrients, vitamins and minerals via the detoxification of the body to the regulation of the hormone balance and blood sugar levels.

Central functions of the liver:

- The liver converts nutrients from the blood so that the body can store them.
- Bile, which is formed in the liver, is essential for the digestion of lipids.
- The liver detoxifies the body. Metabolic decomposition products and toxins are transformed into non-toxic substances, which can then be excreted via the kidneys or intestines.
- Important nutrients are stored in the liver (sugar, lipids, vitamins) and are released to the body's organs and cells, as required.
- The liver controls the level of hormones in the blood, in that it activates or deactivates hormones. The blood sugar level is also regulated by the liver.

Why doesn't the liver inflammation make itself felt through pain?

Pain, the warning signal which is present with many diseases, does not occur with chronic diseases of the liver. There are no nerve fibres, which could convey pain signals, in the liver itself. The destruction of liver cells and the associated inflammation cause the sufferer no pain.

Pain in the area around the liver can occur if the liver capsule (the outer layer of the liver) becomes stressed, in particular, if the liver swells up.

4. The symptoms of acute and chronic hepatitis C

The symptom, which the general public most strongly associates with a hepatitis infection, the yellowing of the skin and mucous membrane (Lat. icterus), rarely occurs with hepatitis C. Also with other viral hepatitis diseases, you cannot simply rely on such supposedly typical yellow colouring.

Both with acute and chronic hepatitis C, symptoms do occur in some patients, such as exhaustion, pain in the limbs, nausea, flatulence, feelings of fullness, epigastric pain, loss of appetite, pale-coloured stools or dark urine; but these are all rather non-specific symptoms. Patients and doctors often do not interpret them as indicating a potential hepatitis C infection, but rather e.g. as the result of overwork or stress.

Even when the doctor has the blood values checked in the laboratory, the hepatitis C infection is then only detected for sure if there is a targeted search for the virus. Liver values, such as ALT and AST, are often increased, but this is not necessarily the case for all patients.

For some patients, hepatitis C can continue without any symptoms for many years; it is only then that the first symptoms appear. As a result of this, chronic hepatitis C often goes undetected for a long period of time. The damage to the liver continues on quietly. By the time the hepatitis C infection has been diagnosed, many patients have already developed the serious long-term consequences of the disease. It is not for nothing that hepatitis C is also called the "silent killer".

5. When the virus affects other organs – extrahepatic manifestations of hepatitis C

Although hepatitis C is a viral disease of the liver, it can also cause diseases in other organs. These diseases and/or symptoms outside the liver are called "extrahepatic manifestations". According to a French study, three-quarters of hepatitis C patients have at least one extrahepatic disorder.^{13–16} The following complications occur relatively frequently:

- Joint and muscle pains
- Kidney damage
- Depression and anxiety
- Changes to the skin and mucous membranes
- Lack of energy and tiredness



Possible, but somewhat rarer symptoms are anaemia (reduced level of red blood cells), diabetes mellitus (generally Type 2), skin and thyroid diseases.

Take-home messages:

- Chronic liver diseases take a similar course when untreated
- The long-term consequences are cirrhosis of the liver and liver cancer
- Symptom-free damage to the liver makes hepatitis C a "silent killer".
- Hepatitis C virus can also trigger symptoms and diseases in other organs. These are called „exhepatic manifestations“.

6. Who should get tested for hepatitis C?

As a general rule, screening for hepatitis C is recommended for following people:¹⁷

- People who have received blood, blood products or organs before an appropriate screening for hepatitis C was introduced [in general before 1991]
- Current or former drug users (intravenous/nasal)
- Patients undergoing long-term dialysis
- Medical staff (healthcare workers)
- Children of hepatitis C infected mothers
- People infected with HIV
- People with increased liver values or other liver diseases

7. Diagnosis: How is hepatitis C detected?¹⁸

Step 1: Detection of antibodies HCV-antibody test

With a hepatitis C infection, antibodies against the virus can be detected in the blood about six to nine weeks after infection. Antibodies are not part of the virus; rather they are created by the immune system as an immune response. A positive test result only indicates that the person has had contact with the virus. It is not possible to differentiate between an acute, chronic or cured hepatitis C infection with an antibody test. If HCV antibodies are detectable, the next diagnostic step takes place.

Step 2: Detection of the virus itself HCV-RNA test

If the virus is still active – a hepatitis C infection is currently present – it is not only antibodies which are detectable in the blood, but also the genotype of the virus (HCV-RNA). A very sensitive test with what is known as PCR (polymerase chain reaction) is then used: a positive test result means that the virus is circulating in the bloodstream at the time of the test. If HCV RNA is detected in the blood, a hepatitis C infection is present.

Exceptions: recent infection

No antibodies can be measured yet for infections, which have only occurred recently. For people with immune deficiencies (e.g. HIV/AIDS), antibodies

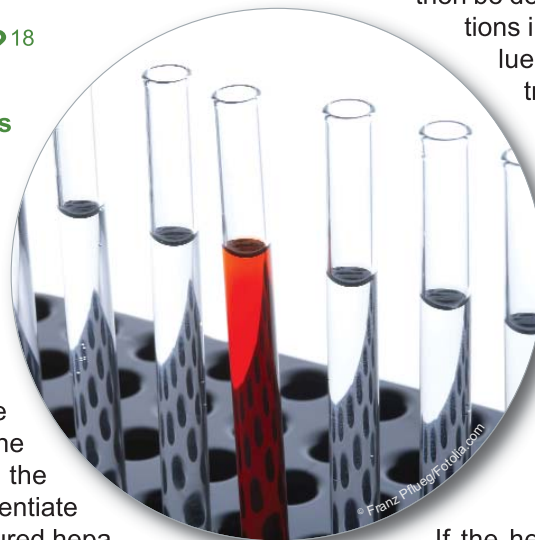
may only appear much later or may not even appear at all. In the opposite case, new-born babies whose mothers are infected can have HCV antibodies in their blood, without themselves being infected.

In these cases, an HCV-RNA test is carried out at once independently of the antibody test. This test is more time-consuming and expensive than the antibody test, but it generally produces reliable results as early as two weeks after an infection.

“Chance diagnosis” – other indications in the blood of an hepatitis C infection

For many patients, there is no targeted search for the hepatitis C virus. A blood count may be carried out due to health problems, or perhaps as part of a routine check-up. Signs of a liver inflammation can mostly be found in the blood with a hepatitis C virus infection. Certain substances are released into the blood by the destruction of the liver cells, which can then be detected in unusually high concentrations in the blood. Two important liver values, which are checked, are the transaminases AST and ALT.

The increase in liver values signals an inflammatory process in the liver tissue. The next step is for the doctor to search specifically for the cause (e.g. hepatitis C virus).



8. A positive hepatitis C test: What happens now?

If the hepatitis C pathogen (HCV-RNA) is detected in the blood, various follow-up tests and corresponding decisions become applicable.

Acute or chronic hepatitis C?

Acute hepatitis C is considered as being easily treatable. Scientists estimate that up to 90 % of patients, for whom a medical treatment is suitable, are able to eliminate the virus.¹⁹ If acute hepatitis C is not treated it then becomes chronic in most patients (50–80 %). One speaks of a chronic hepatitis C, if the virus (HCV-RNA) is still detectable 6 months after the first diagnosis.

How badly damaged is the liver?

After diagnosis, the hepatitis C should still always be tested to determine to what extent the liver tissue has already been damaged. In particular, the condition of the liver plays an important role when considering whether and what type of therapy might be suitable for the patient. If consequences, such as cirrhosis of

the liver or even liver cancer have occurred, they will have a decisive influence on the treatment options, the overall prognosis for the patient and his/her life expectancy.

Various procedures are used in order to investigate the condition of the liver tissue:

- **Other blood values:** In addition to the liver values, AST and ALT, other blood values are determined, e.g. Quick test, gamma-GT, thrombocytes, serum albumin and bilirubin. These values help in estimating the liver's ability to function.
- **Liver biopsy/liver puncture (invasive technique):** A liver biopsy is considered to be a very useful method for establishing the extent of the liver inflammation and any possible scarring of liver tissue (degree of fibrosis).²⁰ In the biopsy, tissue is removed directly from the liver under a local anaesthetic and examined using a microscope. For the majority of hepatitis C patients signs of chronic inflammation can be detected in the tissue. It is an invasive (and therefore a tissue injuring) method which is certainly not regarded as being entirely risk-free and it is also painful for many patients. Complications, such as e.g. haemorrhaging, can occur in a small number of sufferers.
- **Elastography (a non-invasive technique):** Elastography is a relatively new procedure, which can be used to assess the degree of scarring in the liver. Depending on how quickly the sound waves can spread through the liver tissue, conclusions can be drawn about the consistency of the tissue and thus about the degree of scarring. Elastography can replace a biopsy in certain cases – in particular, in combination with blood value results.^{21,22} The devices are not available everywhere, however. For certain investigations a tissue sample is still necessary.

How high is the viral load?

The quantity of viruses present in the blood is described as the viral load (HCV-RNA), which is generally measured in international units (IU) per ml of blood plasma. The higher the viral load, the more viruses are detectable in the blood.

The viral load has no significance for the progress of chronic hepatitis C. Patients with a high viral load do not necessarily have to reckon with a faster pro-



gress. While in the contrary case, patients with a low viral load cannot consider themselves to be in the clear.²³ The measurement of the viral load is nonetheless important for the course of treatment in order to estimate whether a medical treatment should be adopted. Before a course of treatment can be begun, the initial viral load (baseline) must thus be determined. It also serves as an important reference point.

Which viral genotype is the patient infected with?

There are various different genotypes of the hepatitis C virus. Currently, 6 different genotypes of the hepatitis C virus are known. The genotypes each carry different genetic information. Around the world HCV genotypes occur with different frequencies depending on the region. In Europe, types 1, 2 and 3 are the most widespread, while type 1 is the most common HCV genotype.

The viral genotype is decisive for the selection of medications and the length of treatment. To date, genotypes 2 and 3 have been easier to treat and have been cured more often than genotypes 1 and 4. The chances of a successful treatment for genotype 1 have improved greatly recently. And more effective treatments are expected soon for the other genotypes 4, 5 and 6.

Take-home messages:

- Infection with hepatitis C: antibodies (HCV-AB) and the virus (HCV-RNA) are detectable in the blood
- Chronic hepatitis C: viral RNA is still in the blood after 6 months.
- Liver damage is mostly checked by a blood count and a biopsy

9. Treatment of hepatitis C

Overview and history²⁴

As early as 1974 researchers were puzzled by hepatitis infections after blood transfusions, for which neither hepatitis A nor hepatitis B could be the cause.²⁵ The hepatitis C virus, which was responsible for this, was first identified in 1988/89.²⁶ Until then, it was known as “non-A-non-B hepatitis”.

Hepatitis C is curable. The treatment of hepatitis C has made great progress in the last two decades. In the 1990s, the hepatitis C infection was first of all treated with interferon alpha alone. This treatment only had very small prospects of a cure.

Since the late 1990s, interferon alpha was combined with ribavirin. The chances of a cure increased to approximately 40 % with this combination therapy.

A few years later, by using a more effective interferon (peginterferon alpha), the efficacy of the treatment was increased once again. Now 40–80 % of patients treated can hope to be cured. The prospect of a cure was and is, however, still highly dependent on the hepatitis C viral genotype. Patients with the genotype 1, which is most commonly found in Europe, have only approximately a 40–50 % chance of a cure with the combination treatment of peginterferon alpha and ribavirin. Patients with genotypes 2 or 3, on the other hand, have approximately a 70–80 % chance of getting rid of the virus after treatment.

Patients with genotype 1 now have much improved prospects of a cure. The medical authorities in Europe and the USA gave marketing authorisation to two protease inhibitors in 2011. Both substances only act against genotype 1 and must always be combined with peginterferon alpha and ribavirin (“triple therapy”). In many European countries triple therapy is the current standard treatment for patients with genotype 1.

The improved prospect of a virus-free life is however accompanied by many more side-effects and interactions and other therapeutic risks, such as the development of drug-resistant viruses. The triple therapy is very complex. It requires precise planning, great discipline and close cooperation by the doctor and the patient. In order to monitor any side-effects, it is best if the treatment takes place as part of an interdisciplinary cooperation with other specialists (e.g. psychiatrists and dermatologists). Furthermore, the treatment is not suitable for all patients.

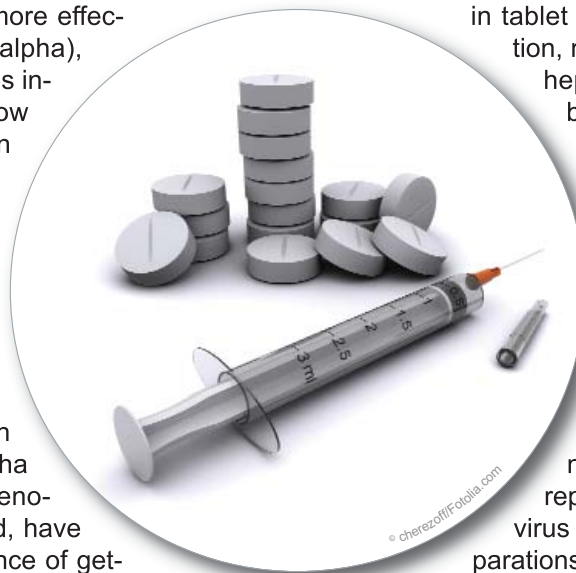
A summary of the active ingredients

Interferon

Interferon is a natural hormone, which is also expressed by the body itself when viruses or bacteria enter the body. Interferon stimulates the body’s natural immune defences. Pegylated interferon is used today. It has a type of protective coating, which prevents it being broken down too quickly in the body. Efficacy can be improved by maintaining constant levels of the medication. Instead of the previous three injections, one injection a week is now sufficient.

Ribavirin

Ribavirin is a virostatic drug and is taken daily in tablet form. As an individual medication, ribavirin has almost no effect on hepatitis C viruses. When combined with interferon, however, it much more frequently leads to a cure of the hepatitis C virus.



Protease inhibitors

Protease inhibitors are known as DAAs (direct acting antivirals). If a specific enzyme is inhibited the virus can no longer produce certain components, which it needs to reproduce. The reproduction of the virus is interrupted. To date, two preparations for treating chronic hepatitis C have been given marketing authorisation in Europe (boceprevir and telaprevir). Both protease inhibitors must be taken with peginterferon and ribavirin and are only effective against the HCV genotype 1. Hepatitis C viruses can become resistant to protease inhibitors.

Treatment schemes

When a treatment is being considered for a patient with chronic hepatitis C today, the type of treatment selected depends, above all, on the viral genotype. Put simply, the current situation is as follows: patients with the viral genotypes 2-6 continue to be treated with the dual therapy of peginterferon alpha and ribavirin. Patients with genotype 1 are treated, whenever possible, with the new triple therapy.

(Data available: 2012)

Similarities between dual therapy and triple therapy

Active ingredients: peginterferon and ribavirin. These two active ingredients are currently still the basis of every therapy for chronic hepatitis C. (Peginterferon is injected 1x weekly; ribavirin tablets are taken daily.)

Treatment goal:

Cure (eradication) of the hepatitis C virus is the goal. Doctors speak of SVR (sustained virological response), this is when the virus can no longer be detected in the blood even half a year after the end of treatment. Patients with SVR are regarded as being cured. After this, it is highly unlikely that the virus will be detected again. This cure can help to prevent secondary diseases, such as cirrhosis and liver cancer.



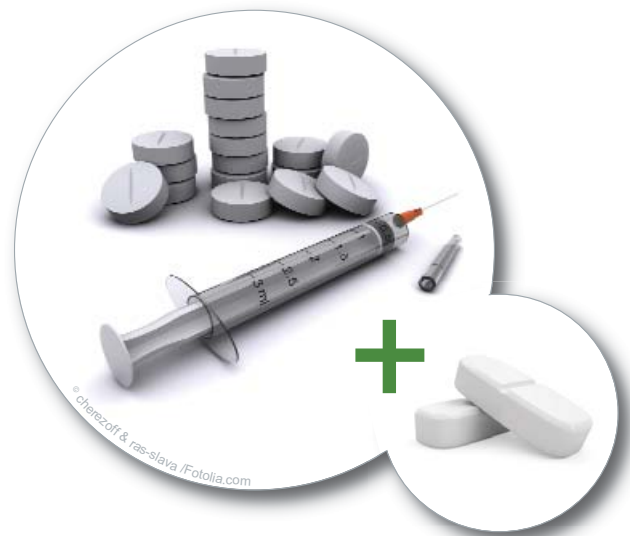
The progress of the treatment depends on response (response guided):

For both the dual therapy and the triple therapy there are various rules on when a treatment can be curtailed or must even be extended for each individual patient (e.g. previous diseases, concomitant diseases, whether the patient has already been treated, the viral genotype or also the quantity of the virus at the start of treatment (baseline "viral load"). Above all, it is vital to measure the viral load at set times during the treatment. If the patient responds well to the medication, this is expressed in a swift and permanent drop in the viral load. Ideally, the virus should no longer be detectable after just 4 weeks. However, if the patient does not react or reacts too slowly, the treatment can be extended or may even have to be discontinued.

Treatment lasts between 24 and 48 weeks for both dual and triple therapies. The dual therapy can be extended to a maximum of 72 weeks.

Many patients with genotype 1 respond quickly to the new triple therapies. In this case the treatment period can often be cut down to 24 – 28 weeks, if there are no other reasons against it (cirrhosis, the individual's treatment prehistory). This is a great step forward in comparison with the previous standard therapy with two drugs, which almost always lasts for 48 weeks for genotype 1 patients.

As yet, only peginterferon and ribavirin are available for genotypes 2 and 3. In this case, however, a 24 week treatment is often enough to eliminate the virus. (Data available: 2012)



Special features of the triple therapy (2012)^{27,28}

Genotype 1 only:

Until now, only patients with genotype 1 could be treated with the triple therapy (both non-pre-treated and pre-treated patients).

It is a combination of three active ingredients:

In addition to the interferon and ribavirin, a protease inhibitor must be taken 3 x daily (every 8 hours) (boceprevir or telaprevir) in the form of tablets and/or capsules.

It is complex and accompanied by many side-effects:

The triple therapy is more complex in comparison with the dual therapy. The medications must be taken almost precisely to the hour and always together with food. Due to the combination of the three active ingredients, patients must furthermore reckon with more frequent side-effects and interactions (see next page).



The therapy's chances of a cure

The chances of a cure differ from person to person. With the dual therapy the prospects of a cure for genotype 2 and 3 patients are between 70 to 80 %. Genotype 1 patients, who undergo a dual therapy for the first time, only have a 40 to 54% chance of a cure. The chance of a cure for these patients increases to 67 to 75 % with a triple therapy. For patients, who have already been treated unsuccessfully with peginterferon and ribavirin, the prospects of success are generally smaller. Genotype 1 patients, who have had a relapse after a dual therapy, are an exception to this: they have a higher chance of a cure with the triple therapy than previously untreated patients.*

Patients with cirrhosis:

Patients with cirrhosis of the liver without restriction of liver function (compensated cirrhosis) can in principle also be treated (depending on the genotype, with a dual or triple therapy). The treatment must be monitored very closely, as the patients are more vulnerable to severe complications. This applies, in particular, to the triple therapy with the three medications. The prospects of a cure are reduced by the cirrhosis. Even after the hepatitis C virus has been cured, the cirrhosis is still present. The risk of liver cancer thus also remains high, and so the organ must still be monitored. The decision for or against a treatment, in particular for patients with cirrhosis of the liver, is always an individual one and depends on the personal benefit/risk ratio.

* The chances of a cure with the triple therapy vary between 31–38 % for previous null-responders to a previous therapy and 75–88 % for previous relapsers. Non-pretreated patients achieve cure rates of 67–75 %.^{29–33}

Treatment side-effects: a potential dilemma for patients

The side-effects of the therapy with interferon and ribavirin can be very stressful for patients. Blood count changes may make it necessary to reduce the dosage of ribavirin. A lower dosage can, on the other hand, have a negative influence on the prospect of a cure. The protease inhibitor dosage must not be reduced due to the danger of resistance; but if side-effects become too severe then the protease inhibitors must logically be discontinued. In some individual cases, it may be necessary to discontinue the treatment entirely. The side-effects can create a real dilemma for patients: they must endure the side-effects or endanger the success of the treatment. The list of potential side-effects is long and ranges from diarrhoea, hair loss to skin rashes and depression. Some of the side-effects which frequently affect patients are listed below:



– Flu-like symptoms

The vast majority of patients suffer, above all, in the initial phase from flu-like symptoms, such as fever, shivering, and muscle and joint pain. The symptoms are caused by the activation of the immune system by the interferon (just as they would also be triggered by the body's own interferon with a "real" viral influenza).

– Depression

More than half of patients experience psychological changes during treatment. For many this expresses itself as mood swings, aggressiveness or impatience, but true bouts of depression can also be triggered by the treatment (and by the disease itself). Susceptibility to depression increases during the

course of the treatment. Absolutely no therapy can be begun if the patient's depression is uncontrollable.

– Fatigue – extremely heavy tiredness

Fatigue can be a side-effect of the medication for treating hepatitis C. Loss of drive, heavy, almost uncontrollable tiredness and insomnia can be truly incapacitating for patients.

– Blood count changes

Blood count changes can occur as a side-effect of the therapy. Levels of haemoglobin, the red blood pigment which is responsible for transporting oxygen in the body, can decline. This anaemia makes itself felt through a shortness of breath, feelings of faintness and problems with concentration. This can be increased still further by the triple therapy. If the number of white blood cells (leukocytes) decreases too far, an increased susceptibility to infection is the consequence. If the number of blood platelets (thrombocytes) is decreased the patient will eventually develop a tendency to bleed easily.

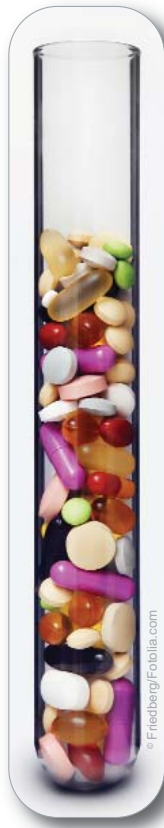
– Skin diseases

Changes to the skin can occur during the dual therapy. In particular, when one of the two active ingredients (telaprevir) is included, skin reactions become more frequent and severe: drying-out of the skin, eczema; or even a powerful itching (pruritus) may occur more often. Individual patients may occasionally experience more severe allergic skin reactions with skin detachments, blistering or dermatorrhagia. In such cases the therapy must be discontinued.

– Teratogenic effect³⁴

Treatment with ribavirin has a teratogenic effect and can cause the development of foetal abnormalities. It must not be used to treat pregnant women and pregnancy must also be prevented by using secure prophylactic methods when undergoing a treatment with ribavirin. This “ban on reproduction” incidentally applies for up to seven months after the end of treatment – and applies to both women and men treated with ribavirin.

According to the prescribing information for ribavirin women must select a secure method of contraception for the therapy period and for up to 4 months after the therapy has ended. Men must use a secure method for up to 7 months after the therapy has ended. In practice some doctors also recommend a waiting period of up to 12 months after the therapy has ended for safety's sake.



– Interactions with other medications

The two protease inhibitors are broken down by a particular enzyme in the liver (CYP3A4/5). Many other medications are also broken down by the same enzyme. This can lead to interactions: medications are broken down more quickly – reducing efficacy – or they are broken down more slowly and too much of the active ingredient builds up. Dangerous side-effects can then occur, just as with an overdose.

Medications, which can interact, range from antidepressants to natural remedies; such as Saint John's wort. This also applies to grapefruit juice, as the naringin it contains can also lead to interactions with the protease inhibitors.

In Europe the University of Liverpool maintains a register of known interactions with hepatitis medications (such as protease inhibitors) at www.hep-druginteractions.org

Treatment failure

Despite improved chances of a cure not all patients who undergo a treatment can be cured. Patients, for whom treatment fails, are subdivided into the following categories:

– Non-responders and null-responders

These are patients, for whom the viral load does not decline sufficiently sharply during the therapy (it is still positive after 24 weeks) or does not decline at all (< 2 log₁₀ decline at week 12). Non-responders react somewhat better than null-responders). Viruses still remain detectable in both groups. The therapy is discontinued early.

– Relapsers

With these patients the virus has been brought below the limit of detection by the therapy, but a relapse still occurs after the therapy has ended. The virus can be detected again.

– Patients with breakthrough

The virus was temporarily undetectable during the therapy, but could then be detected again while the treatment was still continuing. This is relatively rare.

A second attempt at treatment?

Patients, for whom the first therapy was not successful, may consider a second attempt. Patients with a relapse have the best prospects of success. After a dual therapy for genotypes 2–6, a second dual therapy can take place. Furthermore, it is possible for type 1 patients to go on a triple therapy after a dual therapy. Whether the triple therapy can be repeated has not yet been researched and remains an open question.

A new era in treatment? Yes – but not for everyone!

Doctors may talk of a new era in treating chronic hepatitis C. The new therapy options (triple therapy) have made the chances of a cure much more likely. However, the treatment cannot be considered for all patients.

Nor should it be forgotten that the treatments in Europe (and around the world) are also not equally available to all patients. In some countries patients may sometimes have to wait for years for a treatment, which does little to help their situation.

There are also medical reasons that restrict the cohort which can be considered for treatment. The risk of treatment is sometimes too high for patients who have had previous diseases which are associated with similar symptoms (e.g. anaemia or even severe, uncontrollable bouts of depression). It is the same with patients who have other severe diseases (e.g. tumour diseases) or have to take medications, which cannot be tolerated with the protease inhibitors.

The complexity of the treatment, the necessity of taking the medication continually and exactly according to instructions (telaprevir, for example, must not only be taken punctually every 8 hours, but must always be taken together with 20 g of fat), but also the stress caused by numerous side-effects all require a strong desire to be treated, physical stamina and good medical supervision.

The potentially highly debilitating treatment, which in general lasts for 24 to 48 weeks, should be carefully planned. Professional, social, financial or private stress factors do not make a favourable starting point for such a treatment. Such non-medical reasons can also argue against an immediate treatment.

Conclusion: Treatment has become more effective. In particular, patients with genotype 1, who until recently had the poorest prospects of a cure, now have clearly improved chances of a cure. However, serious side-effects and interactions, as well as high treatment costs, still pose problems. Furthermore, in particular the triple therapy cannot be considered for all patients for a variety of reasons.

Treatment of acute hepatitis C³⁵

Acute hepatitis C can, in contrast to the chronic form, be treated with a (peg)interferon monotherapy. If hepatitis C is detected in this early acute stage, up to 90% of cases can be cured. The recommended treatment period lasts for 24 weeks.

Must every case of hepatitis C be treated?

Not every hepatitis C infection must be treated at once. The EASL Guidelines recommend that for patients with chronic hepatitis C in whom the viral disease is progressing only very slowly, therapy should always be considered on an individual basis. The patient's wishes should also play a role in the decision on therapy.

Treatment: Yes or No?

Whether an individual patient begins a treatment or not, is always a highly individual decision. The prospect of a cure is very attractive, but the treatment, which depending on the circumstances can last for almost a year, may have many side-effects and be stressful. Other active ingredients may soon be available in the near future, which will be more easily tolerated and further improve the chances of a cure. It is therefore not an easy decision.

In practice, each patient should consider the following questions before undergoing treatment:

a) Should I undergo treatment?

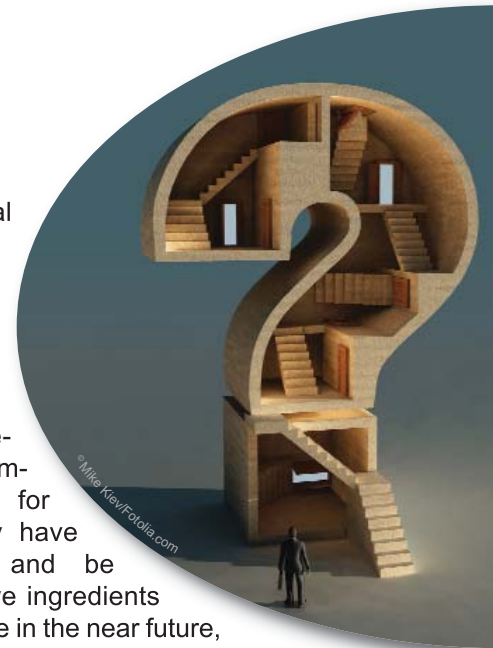
What stage has the liver disease reached? Is there already a danger of liver damage? Am I physically able also to deal with the side-effects and see the therapy through? Can I also stand it mentally? Will my social circle support me? Can I combine my work and treatment? How important is it to me to be "cured" ... ?

b) Can I undergo a treatment?

Can I be medically considered for a treatment? Which genotype do I have? Are there any physical reasons or other medications which argue against a treatment? Do I have access to a suitable treatment (geographically, financially...)?

c) What chances do I have of a cure?

Not all patients have equally good chances. It depends on numerous factors, such as the genotype, previous diseases and also age. It is important to recognise the individual's treatment prospects in order to make an informed decision.



What is the situation with additional and alternative treatment options?

A cure using alternative or natural remedy methods, as is possible with an antiviral therapy, cannot be expected for chronic hepatitis C. To what extent certain herbs or dietary supplements are beneficial for hepatitis C is still a matter of debate. Particular caution is always advisable when exaggerated claims of a cure are made.

Food supplements:

Dietary supplements are a subject of controversy. The additional intake of vitamins and minerals – such e.g. a combination of vitamin D and calcium - can be helpful with a vitamin deficiency, but this should be discussed with a doctor. In most cases this is not necessary. Ideally, vitamins should be consumed as part of a healthy diet. At high doses, in particular vitamin A can incidentally have a damaging effect on the liver.

Milk thistle

Preparations made with milk thistle are popular with many liver patients and are also taken by many hepatitis C patients. The efficacy of silibinin as an infusion solution is well-proven, but silymarin in the form of tablets or capsules is of rather doubtful efficacy. In 2011 an independent study showed that silymarin capsules even at 4 to 7 times the normal dosage had no more effect than a placebo: neither the liver values, viral load nor the quality of life were influenced.³⁶

Infusions with silibinin, on the other hand, have a powerful, albeit temporary antiviral effect against he-



patitis C. Further research is being carried out in connection with interferon therapies and liver transplants.^{37,38}

Traditional Chinese medicine, homeopathy, anthroposophy

Healing methods, which deviate from conventional forms of medical treatment, are also rarely examined in scientific studies. Their efficacy is therefore a matter of controversy. If alternative forms of treatment are chosen, the patient should consult with a reputable qualified therapist.

The ingestion of active ingredients of any kind should always be discussed with the patient's doctor in order to exclude any potential harmful effects on the liver and interactions with other medications.

We do *not* recommend the often-suggested practice of "liver cleansing". Human faeces change colour and become clumpy with an unfamiliar diet of olive oil and juices. Patients are persuaded that the discoloured and hardened faecal clumps are successfully excreted "gallstones".^{39,40}



Warning! Care should be taken with many so-called "hepatoprotective mixtures", "liver cures" or "miracle cures". In some cases they can cause severe or even fatal side-effects (e.g. LIV.52, shosaikoto, Miracle Mineral Solution).⁴¹⁻⁴³

10. Future forms of treatment

Numerous, and occasionally severe side-effects, complex instructions for taking the drug, hazardous interactions: these are not the only disadvantages of the currently available therapy options for dual or triple therapy. Research into new forms of treatment is proceeding in different directions. How quickly effective and safe new therapy options will be available, still remains to be seen.

Triple therapies with new DAAs (e.g. protease inhibitors and polymerase inhibitors)

It is hoped that therapies can be developed which will cause fewer side-effects and have better prospects of a cure, will not only be limited to geno-

type 1, and can be used with simpler instructions for taking the drug. It is likely that these will initially be approved as a triple therapy with peginterferon and ribavirin.

Interferon-free therapies with DAAs:

Until now, in particular, interferon was thought of as the "backbone" of any hepatitis C therapy. As many side-effects are caused by interferon, the development of an interferon-free therapy would be a great step forward. Also for the patients, for whom an interferon treatment cannot be considered – e.g. due to previous diseases or advanced cirrhosis of the liver. Research is being carried out on combinations of several direct acting antivirals (DAAs) with and without ribavirin. The first interferon-free cures of hepatitis C

were achieved in clinical trials in 2011. The first interferon-free therapies could be available from 2015.

Quadruple therapies (therapy with four drugs):

Patients, who have previously proved very difficult to treat (e.g. non-responders and null-responders), could benefit from the combination of peginterferon and ribavirin with two antiviral active substances. It may also be possible to shorten the overall therapy period, although even more serious side-effects may have to be taken into account in such cases.



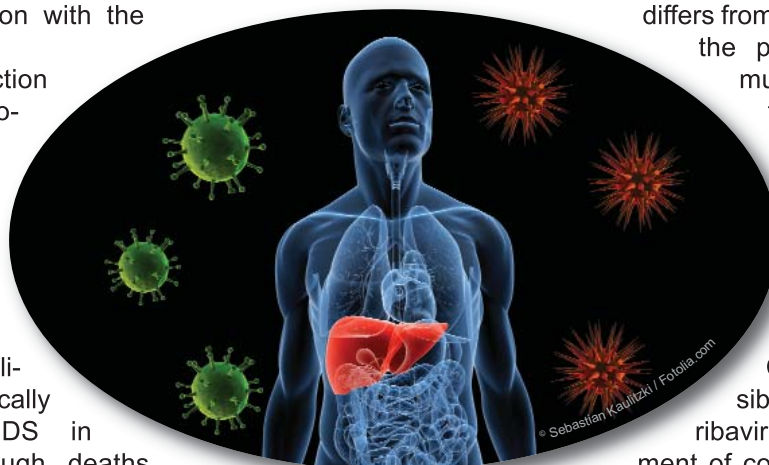
Take-home messages:

- Therapy depends on the genotype
- Dual therapy for types 2-6, triple therapy for type 1
- Response-guided therapy
- Treatment is complex for patients and doctors
- Serious side-effects and interactions are possible
- Up to a 80% chance of a cure
- Alternative methods of treatment have had very little testing and their efficacy is a matter of controversy
- New treatments for hepatitis C are being researched

11. Hepatitis C and HIV (co-infections)

Hepatitis C now poses one of the most serious clinical challenges to patients with HIV. Almost a third of all people infected with HIV in Europe have a concomitant infection with the hepatitis C virus.⁴⁴

A concomitant infection with the HI virus (co-infection) accelerates the progression of hepatitis C. As HIV treatment itself has made great progress in the last few years and decades, there are now far fewer fatalities from diseases typically associated with AIDS in Europe today; although deaths caused by hepatitis C amongst people infected with HIV have increased. Cirrhosis and liver cancer occur much more quickly in patients with HIV and HCV.



Doubly-infected mothers have a significantly higher risk of infecting their babies with hepatitis C while giving birth. Conversely, however, an infection with hepatitis C appears to have little effect on the progression of an HIV infection.

The treatment of chronic hepatitis C for patients concomitantly infected with HIV principally differs from the dual therapy in that the period of treatment is much longer. To what extent the new substances in the triple therapy can also be used, is currently being researched. Severe and even fatal interactions between certain HIV and hepatitis C medications are possible (e.g. didanosine and ribavirin); therefore, the treatment of co-infections should only be carried out by experienced doctors.

Due to the high rates of double infections, patients with HIV should also have themselves tested for an infection with the hepatitis C virus.

12. Hepatitis C and liver transplants

Cirrhosis of the liver due to hepatitis C is a frequent reason for liver transplants. Even some liver cancers can, if they are detected early enough, be cured with a transplant. Transplantation is thus mostly the *ultima ratio* – i.e. the final treatment option.

The therapy goal for chronic hepatitis C is thus to eliminate the virus promptly before irreparable damage to the liver has occurred. Liver transplantation is still a serious and highly risky intervention, even if mortality and morbidity rates are clearly improved after transplantation.

Patients with chronic hepatitis C generally receive transplants if their life expectancy is clearly reduced due to liver dysfunctions – and, if a suitable donor organ is available. In Europe organs are allocated in accordance with urgency (in precedence over waiting time): whoever is at the greatest risk of dying will receive the next organ which becomes available.

Chronic hepatitis C cannot be cured by a transplant. For almost all patients with an active virus at the time of transplantation a renewed infection of the donor organ (reinfection) occurs within just a few hours. The disease may take different courses after the transplant. In contrast to patients who do not receive a transplant, the disease advances more quickly with a high viral load.⁴⁵ A third of patients develop cirrhosis again within 5 years.⁴⁶

Liver-transplant patients with chronic hepatitis C can in principal be treated with the dual therapy. Chances of a cure from dual therapy with the two medications are only about 15–25 %. Particular attention must be paid to potential rejection reactions.

The prospects of a cure can be improved if a therapy is begun before the transplant takes place. If the viral load can be brought below the limit of detection before the transplant (HCV-RNA clearance), no re-infection of the donor organ occurs in three-quarters of patients.⁴⁷



This approach can only be considered for a small number of patients due to restricted liver function or other contraindications before transplantation.

To what extent a triple therapy with three medications might be successful and feasible for liver transplant patients, is currently the subject of research. On the one hand, the response rates could be improved. On the other hand, one must be aware of dangerous interactions, which might occur between the antiviral medications (DAAs) and the immunosuppressant medications. Immunosuppressants suppress the immune system and prevent the new organ from being rejected by the body after transplantation. The effective levels of some immunosuppressants in the blood serum can be increased many times by interactions with the DAAs. Thus, such a treatment should only take place in clinical trials and in specialist centres. In particular, new, more easily tolerated forms of treatment would be of great importance for these groups of patients who are difficult to treat, such as e.g. an interferon-free therapy.

The problem remains in this context, however, that liver transplant patients cannot participate in the marketing authorisation trials due to the increased risks involved (even if they expressly wish to do so). This means that those affected will have to wait quite some time until it is certain whether a new therapy can also improve the situation for patients after transplantation. Time is, of course, precisely what they are lacking.

Take-home messages:

- Hepatitis C occurs frequently in people infected with HIV
- An HIV infection accelerates the progression of the liver inflammation
- Hepatitis C therapy is possible with an HIV co-infection, and one should be aware of drug interactions
- Liver transplantation is the “ultima ratio” for liver diseases
- Re-infection of the donor organ can occur within hours
- A cure through transplantation: this is only possible with HCV-RNA clearance before the intervention
- Treatment of an HCV infection is also possible after a liver transplant

13. Stigmatisation: still a great hurdle

Hepatitis C is a stigmatised disease. Prejudices, unfounded anxieties and false information are common not only in the general population and public opinion. Hepatitis C sufferers are often stigmatised even in specialist medical circles. Many sufferers find this harder to bear than the symptoms of their disease.

Hepatitis C – not just a disease of drug addicts

Hepatitis C can affect anyone. At the same time many drug users (even former drug users) have hepatitis C, as it can be transmitted by the shared use of needles and other drug paraphernalia. In Europe it is estimated that 70 % of people who take



drugs intravenously have already come into contact with the hepatitis C virus.⁴⁸ Conversely, however, absolutely no conclusions can be drawn on the basis of a hepatitis C infection that someone has a background of drug-taking or is still a drug user.

Many patients have contracted the disease from infected blood transfusions, medications made from blood plasma, through unclean medical interventions, needle-stick injuries in the medical sphere, birth, sexual partners or via other transmission paths. Sexually-transmitted infection is relatively rare; the risk is only clearly increased by practices that tend to cause injuries and by intercourse during menstruation.

The path of transmission simply cannot be reconstructed for a large number of patients. Such cases may well involve a forgotten or unnoticed contact with blood.⁴⁹

Hepatitis C – false dramatization of the risk of infection

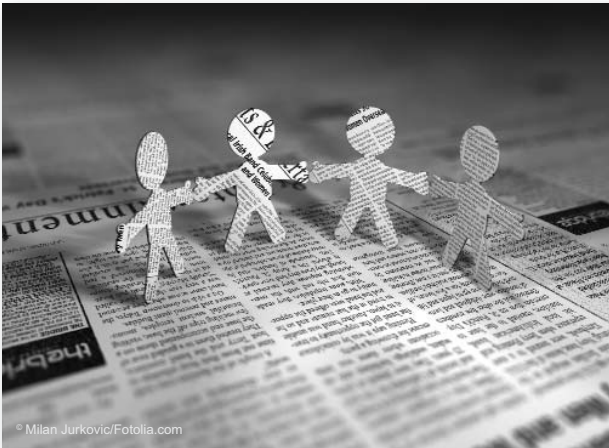
Patients with hepatitis C are often excluded from their social circle by colleagues, neighbours and acquaintances. Sufferers report that people in their social circle even recoil from normal everyday physical contact, such as hugging or even shaking hands – out of an exaggerated fear of infection. Hepatitis C is however not transmitted by droplet infections, as influenza can be, for example. Nor are smear infections possible, as is the case with hepatitis A. As long as there is no contact with blood, an infection with hepatitis C is excluded for all practical purposes (cf. Chapter 2 “Transmission and protection from hepatitis C”, page 5).



Stigmatisation through lack of attention. Hepatitis C in the media

Hepatitis C receives almost no media attention. Most people have very little idea about the functions of the affected organ, the liver, and what it actually does. The progression of hepatitis C – which itself goes unnoticed by most sufferers for years or even decades – causes no symptoms for a long time. It is only in the final stages that dramatic consequences, such as vomiting blood, ascites, liver cancer, organ failure and coma occur. Until such serious secondary diseases appear, hepatitis C is virtually invisible.

The numbers of those infected has also remained virtually unchanged. In Europe 9 million people are still infected with the hepatitis C virus.⁵⁶ [In comparison: the number of people infected with HIV in Europe is estimated by the WHO to be 2.3 million.⁵⁰] Almost 90,000 people in Europe die each year from the consequences of hepatitis C.⁵¹ It is estimated that 90 % of those currently infected are completely unaware that they have hepatitis C.⁵² It would also be very helpful in this context if there were greater



public enlightenment about hepatitis C. There is still far too little discussion of the “silent killer”: hepatitis C – particularly in the mass media.

That the subject of hepatitis C hardly ever appears in the media, further contributes to the stigmatisation of the disease. The media could make a real contribution to giving hepatitis C a face and overcoming prejudices. Hepatitis C can theoretically affect anyone, regardless of background, age or lifestyle, although one can protect oneself effectively from an infection by taking simple precautionary measures.

Stigmatisation: practical consequences for sufferers

Experiencing social exclusion or the fear of it affects patients with hepatitis C and also confronts them with practical problems. On the one hand, for example,

doctors looking after patients often advise them not to be too open about the diagnosis of chronic hepatitis C and to consider carefully whether work colleagues should even be told*. There is always the potential danger of exclusion and discrimination.

On the other hand, patients, who are about to undergo a medical therapy, also need support and understanding from those around them. A 24 to 48 week therapy, which may be accompanied by many side-effects, is very hard to keep secret. Patients, who are treated with the new triple therapy, due to the numerous potential side-effects are explicitly recommended to include their social circle and, above all, also to explain about any possible psychiatric changes (ranging from irritability to severe depression). More support for the patients, who are already stressed, and a type of “early-warning system” for any psychological changes – is the positive idea behind this. And it is all too easy to forget about the social milieu in which many sufferers of hepatitis C actually live.

* Everyone infected with the hepatitis C virus should tell (sexual) partners, anyone with whom they share a house, and anyone who may come into contact with their blood (e.g. doctor/dentist/first-aider), about an existing HCV infection, so that they can consciously protect themselves from coming into contact with infected blood. There is also normally a legal obligation to inform sexual partners. In terms of employment, if there is no increased risk of infection in the workplace, then it is not normally absolutely necessary to inform work colleagues – although laws and obligations on disclosure can vary from country to country in the EU.

Take-home messages:

- Hepatitis C patients are frequently stigmatised
- This is due to ignorance, prejudice and a dramatization of the risk of infection
- There is too little awareness in the media

14. Living with hepatitis C

Nutrition:

No special diet is necessary if liver function is not yet restricted. A well-balanced and healthy diet is recommended. Patients should avoid becoming overweight; and abstinence from **alcohol** and **nicotine** is important in order not to cause the liver additional stress.

Medications:

Some medicines can lead to an increase of liver values. All patients with chronic liver diseases should avoid any unnecessary medications. Interactions with protease inhibitors taken as part of the triple therapy are of particular importance.

For people with other serious diseases (aside from the hepatitis C) the situation is especially difficult: sometimes certain medicines must be taken, although they will cause additional stress to the liver. Medical advice should be sought in such cases.



Coffee seems to have a positive effect on the liver. Studies have shown that long-term consequences, such as cirrhosis and liver cancer, occur more rarely or later in coffee drinkers with hepatitis C.⁵³ In contrast with coffee, green tea has no influence of the progression of hepatitis C.⁵⁴

Hepatitis C patients can, as long as they can tolerate it, be advised to drink coffee. It is only with cirrhosis of the liver with complications that it can be necessary to restrict certain foodstuffs, such as e.g. common salt and fluids due to ascites. This must be discussed on an individual basis with a doctor or nutritionist. A "low-protein" diet is only recommended very rarely today, as this increases muscle loss and often makes the progression of the disease worse.⁵⁵ Patients with cirrhosis, however, can often tolerate plant-sourced protein, e.g. from vegetables, better than animal protein from meat products.

Work
There are no unified European regulations on hepatitis C and the workplace. People with chronic hepatitis C can generally work freely in all professions and there is no need to change jobs. There are restrictions, above all, in professions with a high risk of infection or injury (e.g. abattoir workers) and in certain medical fields (e.g. surgery).

Self-help: patients helping patients

The concept of self-help – sufferers helping other sufferers – is a valuable and helpful one for many chronically ill patients, and it is also appreciated by many hepatitis C patients. In European countries there are numerous hepatitis C self-help groups, in which sufferers can exchange information about the disease, therapy and other practical questions and provide mutual support to one another in overcoming the disease.

Addresses can be requested from national patient organisations. More information is available from the European Liver Patients Association (ELPA): www.elpa-info.org

15. Statistics for hepatitis C: the situation in Europe and the rest of the world

Europe

- In Europe c. 9 million people are infected with the hepatitis C virus.⁵⁶
- 86,000 people die from its consequences every year.⁵⁷
- c. 29,000 new cases of hepatitis C are diagnosed annually – the trend is rising.
- The prevalence (the frequency of the disease in relation to the total population) in Europe varies between the individual countries from 0.1 % in Belgium to 2.6 % in Italy, while some regions, such as Sicily, report rates over 8 %.

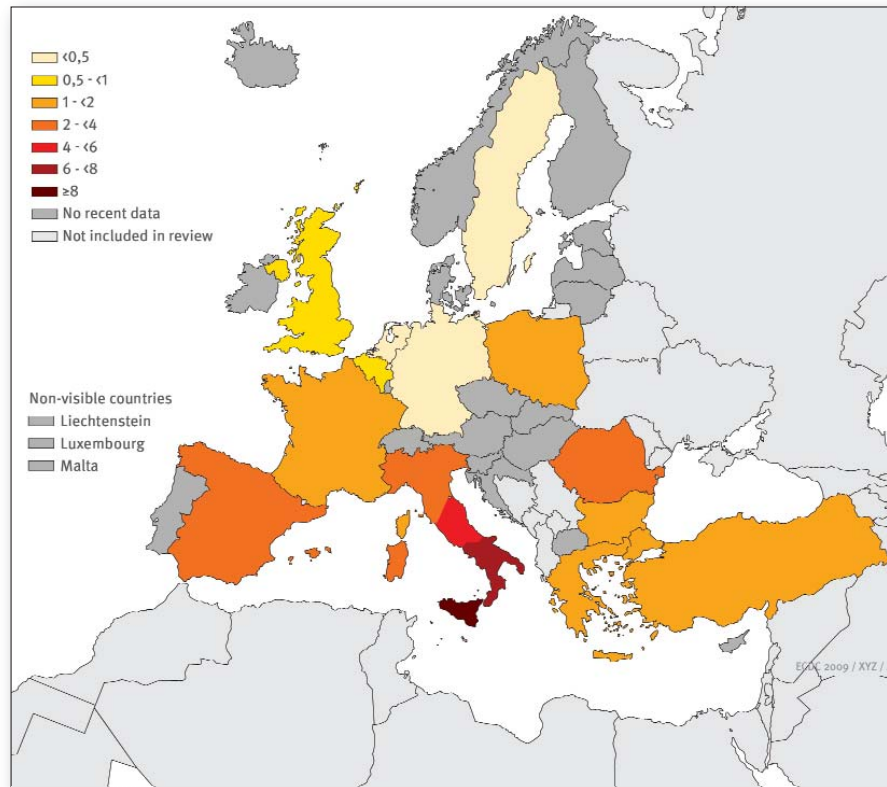
The problem with statistics

Statistics and epidemiological data on the distribution and frequency of hepatitis C must be regarded with a certain degree of caution. In particular, it is hard to draw comparisons between countries. The reason for this is the insufficient level of data available, on the one hand, and the different methods of recording data in the individual countries, on the other hand.

Liver cancer

In particular, between the 1980s and 1990s there was a sharp increase in mortality due to liver cancer; in part with a continually increasing tendency. Around the world liver cancer is the third most common cause of deaths due to cancer.⁵⁹

Liver cancer, in a majority of cases, is the consequence of a chronic viral hepatitis B or C. In Italy, 82 % of liver cancer patients are infected with hepatitis B (18 %) or C (64 %). While in many countries hepatitis C is proportionately dominant amongst liver cancer patients; it is the opposite case in Turkey and Greece.⁶⁰



Hepatitis C: prevalence in the general population
North-South divide: hepatitis C occurs much more frequently in Mediterranean countries than in Northern Europe. (ECDC 2010)⁵⁸

The situation around the world^{61,62}

- Depending on the estimate, 150–200 million people are infected with chronic hepatitis C.
- Approximately 3–4 million new infections occur annually.
- More than 350,000 people die from its consequences each year.
- The prevalence (rate of disease) ranges from 0.4 % in Central and Northern Europe via 3.2 % in China, 4.8 % in Pakistan up to 22 % in Egypt.*
- In particular, in developing countries expensive therapies are not available to most sufferers.

* The hepatitis C virus was frequently transmitted while combatting schistosomiasis in Egypt between 1950 and 1980; this was presumably due to the multiple use of insufficiently disinfected cannulae. The number of people affected is estimated to be about 6 million. This explains the unusually high prevalence of up to 22 % in Egypt.⁶³

Take-home messages:

- People infected with hepatitis C: 9 million in Europe, up to 200 million world-wide.
- Hepatitis C is now the main cause of liver cancer in Europe today

16. Political dimensions

In Europe c. 9 million people are infected with the hepatitis C virus. Almost 90,000 people die from its consequences every year.⁶⁴ Although chronic hepatitis C is one of the most dangerous infectious diseases anywhere in the world, little effort has been made in terms of healthcare policies by the different nations – and it is the same at a pan-European level. Viral hepatitis does not appear on the “radar” of the political decision makers. Viral hepatitis has no strong lobby group and the general public are not sufficiently aware of the threat posed by this “silent killer”. Hepatitis C also receives very little coverage by the mass media and is under-represented in comparison with other (viral) diseases (there are 9 million people infected with hepatitis C in comparison with 2.3 million people infected with HIV in Europe, for example).⁶⁵

In the context of prevention and policies on disease control there are two distinct prevention strategies – primary and secondary prevention.

Prevention strategies (as defined by the WHO)⁶⁶

– Primary prevention:

Primary prevention is directed towards preventing hepatitis C from spreading any further. Protection from infection through information is given priority. Hygiene measures in the medical sphere likewise play an important role.

– Secondary prevention:

Secondary prevention concentrates on improving the situation of those who are already infected with the hepatitis C virus. Early diagnosis of hepatitis C, targeted screening within at-risk groups, shortening the duration of the disease: these are the goals of secondary prevention.



17. Patient and self-help organisations in Europe⁶⁷

The activities of patient and self-help organisations in the individual European countries are many and various. Increasingly important is the political function, which the European self-help organisations can carry out at a national level within the respective healthcare systems. In particular, this is because it is the patients themselves who are looking at and encouraging activities relating to both primary and secondary prevention.

A summary of their main functions:

– Supporting patients:

Self-help organisations primarily undertake the support of other patients and their families. Their political functions have not altered this. Along with factual information and advice, there is a focus on providing psychological support. The latter is often neglected



by healthcare systems. European EASL Guidelines on the supervision of mental disorders associated with hepatitis C, which were initiated due to pressure from ELPA, are expected in the near future.

– Providing training to achieve higher rates of diagnosis:

Some self-help organisations are also involved in the training and further education of medical healthcare professionals.

GPs and family doctors are especially key figures. Although they are not liver specialists, they still have an important role to play in screening for hepatitis C. Against a background where an estimated 90% of people infected with hepatitis C are unaware of their disease, family doctors are in a very special position. They come into closest contact with the patient and they are the first to be confronted with the diffuse symptoms of a viral hepatitis. The next step lies with them, as they can check the liver values in the blood count and then set the next diagnostic steps in motion.

Increasing public awareness:

Public awareness of viral hepatitis C is very low. Only about 20 % of hepatitis C patients in Europe, according to one study, had even heard of the hepatitis C virus at the time of their infection. Only a quarter of infected patients regarded themselves as belonging to an at-risk group.⁶⁸ Most of them did not know that

they personally had an increased risk. These results should serve as a wake-up call: they show how little is known about hepatitis C. Awareness-raising programmes are oriented both towards people who belong to the at-risk groups and the public at large. In terms of content such programmes can go a long way towards destigmatising hepatitis C.

Take-home messages:

- 90 % of people with hepatitis C do not know that they are infected
- Rates of diagnosis must be increased
- The media and general public must be more aware of the “silent killer”: hepatitis C
- Self-help organisations play both advisory and political roles

Important terms and glossary

Anaemia: Iron deficiency. Levels of the red pigment in the blood (haemoglobin) can be reduced by chronic hepatitis C, cirrhosis of the liver, and also by the HCV therapy. The transport of oxygen in the blood is affected and this often causes a shortness of breath, feelings of faintness and problems with concentration

Biopsy: Tissue is removed from the body – e.g. with a long cannula – under a local anaesthetic and then examined under a microscope. A liver biopsy is still regarded as the most informative procedure for establishing the degree of scarring of the liver (degree of fibrosis) and the extent of the liver inflammation with chronic liver diseases.

Blood-to-blood transmission (blood-borne disease); Hepatitis C is a “blood-borne disease”, i.e. a disease which is transmitted by blood. While with other viral diseases, such as hepatitis B or HIV, other transmission paths play a large role (e.g. sexual transmission); the hepatitis C virus is almost exclusively transmitted by infected blood.

Cirrhosis: Chronic liver diseases can lead to a scarring of the liver. This scarring process is called fibrosis. Cirrhosis is the final stage of the scarring process. This is when structural disorders of the liver tissue occur, which can lead to a loss of liver function. Frequent causes are viral hepatitis, alcohol, liver-damaging substances or metabolic and autoimmune diseases. The liver can continue to function with a compensated cirrhosis. If functional disruptions and complications occur, then this is called a decompensated cirrhosis.

Co-infection: Simultaneous infection with two pathogens, e.g. hepatitis C and HIV; in contrast to a mono-infection (an infection with one pathogen). With a superinfection there is an infection with a new pathogen in addition to an existing chronic infection (e.g. a patient with chronic hepatitis C contracts an additional infection with hepatitis B).

Extrahepatic: Does not affect the liver or has an effect outside the liver (opposite term: hepatic). Other organs in the body can be damaged by the virus through extrahepatic manifestations of hepatitis C (e.g. kidneys). Symptoms such as depression can be a consequence of a chronic Hepatitis C infection.

Fibrosis: Liver cells can be converted into functionless stroma and connective tissue as a consequence of a chronic liver inflammation. This scarring is called fibrosis. Fibrosis is a precursor stage to cirrhosis of the liver.

Genotype: Currently 6 different genotypes of the hepatitis C virus are known (genotypes 1 – 6), which each have different subtypes (e.g. genotype 1a and 1b). The viral genotype influences the choice of treatment with hepatitis C and the prospects of a cure. It seems likely that the HCV genotype has little or no influence of the progression of the disease.

HCV: Abbreviation of the hepatitis C virus. After an infection with the hepatitis C virus the genotype of the virus (HCV-RNA) can be detected in the blood. After a short period the immune system produces antibodies against the virus (HCV-AB), which are then likewise detectable in the blood. If HCV-RNA and HCV antibodies can still also be detected after 6 months, then the hepatitis C has become chronic. If the hepatitis C has been cured (a natural

self-healing or due to treatment), no viral genotype is any longer present in the blood. Antibodies, on the other hand, are still detectable in the blood years later.

Hepatocellular carcinoma (HCC): Liver cancer and/or liver cell cancer. This is a malignant tumour disease and long-term complication of chronic inflammation of the liver. Chronic viral hepatitis is the most common cause of liver cancer. For patients with chronic hepatitis C, liver cancer generally only occurs when cirrhosis is already present. With chronic hepatitis B, on the other hand, the malignant tumour can form in the liver even without cirrhosis having previously occurred.

Icterus: Yellowing of the skin and mucous membranes. Icterus is a fairly rare occurrence with hepatitis C. The symptom is more commonly observed with a severe acute progression or as a consequence of cirrhosis of the liver.

Incidence: See Morbidity

Limit of detection: The lower limit of detection is a standard measure for a test procedure. It describes the lowest concentration which can still be detected by the test system. HCV measurements under the limit of detection are generally declared to be “negative”, which is not quite correct, as the HCV-RNA can still be present in a low concentration below the limit of detection. It is only when the virus concentration is still below the limit of detection six months after a therapy that a cure can be assumed.

Morbidity: Morbidity is the frequency of the disease in a particular section of the population. Morbidity is an umbrella term for the prevalence (the rate of those who are already infected) and the incidence (the rate of new infections within a set period of time) of a disease.

If one wishes to investigate the number of new infections in a particular period (e.g. in one year), then this is the incidence. All indices are referenced to a particular population: e.g. against the entire population or per 100,000 inhabitants.

For example: in 2010 the incidence of hepatitis C in Germany was 6.5 per 100,000 inhabitants. [A new diagnosis of hepatitis C is calculated to have been made for 6.5 inhabitants per every 100,000 inhabitants during that year.]

The prevalence of hepatitis C was 0.4% in Germany in 2010. [0.4% of the total population is infected with the hepatitis C virus at the time of the measurement.]

Mortality: Rate of fatalities. Statistical size of the epidemiology. Mortality describes the number of fatalities in relation to a population (e.g. total population or a group within the total population, such as “men”).

For example: in 2010 the mortality for men in Hungary due to cirrhosis of the liver was 68 out of 100,000. [For every 100,000 men, who died in Hungary in 2010, cirrhosis of the liver was the cause of death in 68 men.]

Peginterferon: This medication is injected to treat hepatitis C (as a rule 1x weekly). Interferon stimulates the immune system so that it can fight the hepatitis C virus more effectively. Interferon is combined with ribavirin to treat chronic hepatitis C. In the new triple therapy (for genotype 1) interferon is combined with ribavirin and a protease inhibitor.

The most frequent side-effects of interferon are flu-like symptoms, blood count changes and depression.

Prevalence: See Morbidity

Protease inhibitors: Protease inhibitors are active ingredients which inhibit an enzyme of the hepatitis C virus and thus directly hinder the virus from reproducing. In 2011 two protease inhibitors (boceprevir, telaprevir) were licensed by the EMA (European

Medicines Agency) for the treatment of chronic hepatitis C in the EU. The therapy is carried out exclusively in combination with peginterferon and ribavirin (see triple therapy). Furthermore, it is only possible for patients with the viral genotype 1.

Response: Response to a therapy. Present-day forms of therapy for chronic hepatitis C are response-guided, i.e. therapy is guided by whether and how quickly a patient responds to the treatment. The development of the viral load is decisive for the treatment of hepatitis C. Different types of response can be distinguished:

- **Rapid virological response (RVR):** The viral load declines very quickly at the start of the therapy and also remains below the limit of detection during the course of the therapy.
- **Delayed virological response (DVR):** The viral load declines only slowly, but then remains below the limit of detection.
- **Non response / partial response:** The viral load declines in part, but always remains detectable. The therapy with peginterferon and ribavirin is then discontinued due to its ineffectiveness after 24 weeks.
- **Null response (NR):** The viral load is not reduced or only declines slightly and always remains detectable. The therapy with peginterferon and ribavirin in this case is discontinued due to its ineffectiveness after twelve weeks.
- **Breakthrough (BT):** The viral load had already fallen below the limit of detection. The virus suddenly becomes detectable again during the therapy. [An increase in the viral load after the therapy has ended is a relapse, see
- **Relapse:** This is a renewed occurrence of the disease. If a patient is free of the virus when the therapy ends (the viral genotype cannot be detected), but the virus can be detected in the blood again some time later, then this is called a relapse. It is assumed today that a patient is cured if no relapse occurs within 6 months after the therapy coming to an end.
- **Sustained virological response (SVR):** No virus is detectable any more 6 months after the therapy has come to an end. The hepatitis C is considered to be cured.

Ribavirin: Ribavirin is a medicine, which is administered in addition to interferon to treat chronic hepatitis C. It increases the efficacy of the interferon therapy. Hepatitis C cannot be treated by ribavirin alone. Anaemia (iron deficiency) is a frequent side-effect of ribavirin

SVR: Sustained virological response: long-term successful treatment of hepatitis C. HCV-RNA still cannot be detected in the blood six months after the therapy has ended. The hepatitis C is regarded as being cured. Later relapses are rare.

Triple therapy: In this type of therapy three medications are used in combination against chronic Hepatitis C: these are currently peginterferon (injection), ribavirin (tablets) and a protease inhibitor (tablets).

As yet, it is exclusively patients who are infected with the viral genotype 1 that can be treated with the triple therapy. Triple therapy improves the chances of a cure for these patients sometimes quite considerably, but it is also associated with many side-effects. The treatment period lasts between 24 to 48 weeks, depending on the patient.

Viral load (HCV-RNA): The viral load gives information about the quantity of hepatitis C viruses which are detectable in the blood. It is mostly measured in international units per ml of blood; the previous measurement was copies per ml of blood. The advantage of a measurement in IUs is that the measurement results from various tests can be compared. The extent of the viral load has no connection with the progress of the disease for chronic hepatitis C (except for patients who have had a liver transplant or patients with an HIV co-infection), although the extent of the viral load can have an effect on the prospects of a cure with a medical treatment.

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