

HCSP TRAINING MANUAL

SECTION VI: HCV SYMPTOMS AND PROGRESSION

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The information in this guide is designed to help you understand and manage HCV and is not intended as medical advice. All persons with HCV should consult a medical practitioner for diagnosis and treatment of HCV.

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A publication of the Hepatitis C Support Project

HCV SYMPTOMS AND PROGRESSION

Objectives:

- *Be able to describe acute and chronic hepatitis C*
- *Be able to describe the symptoms of hepatitis C*
- *Be able to describe possible long-term liver damage due to HCV*
- *Be able to distinguish between compensated and decompensated cirrhosis*
- *Be able to discuss several conditions associated with advanced HCV*

HCV Symptoms and Progression

HCV Symptoms and Progression: Key Points

- *HCV attacks liver cells.*
- *The immune system responds to the hepatitis C virus infection.*
- *Acute hepatitis C is the initial stage of HCV disease.*
- *Chronic hepatitis C is when HCV persists for more than six months.*
- *Chronic hepatitis C occurs in 55% - 85% of people infected with HCV.*
- *Symptoms of hepatitis C may include flu-like illness, fatigue, nausea, loss of appetite, fever, headaches, abdominal pain, and muscle or joint pain.*
- *Many people with acute and chronic hepatitis C experience no symptoms.*
- *10-25% of people with chronic HCV experience progressive liver disease.*
- *HCV progression usually takes years or decades.*
- *Steatosis or fatty liver contributes to HCV disease progression and lower HCV treatment response rates.*
- *Liver damage due to HCV may include cirrhosis and liver cancer.*
- *People with decompensated cirrhosis may develop complications such as portal hypertension, bleeding varices, and ascites.*
- *Various conditions are associated with late-stage HCV disease.*
- *HCV is the leading reason for liver transplants in the U.S.*

HCV Symptoms and Progression:

General Information

Acute HCV

HCV attacks liver cells. After exposure to the virus, there is a window period that usually lasts 2-26 weeks. The initial phase of HCV disease is called acute hepatitis C. Many people with acute HCV infection have no symptoms. Others may experience flu-like illness, fatigue, nausea, vomiting, diarrhea, indigestion, loss of appetite (anorexia), fever (sometimes accompanied by night sweats), headaches, abdominal pain or bloating, and muscle and joint pain. Some develop jaundice (a yellowing of the skin and whites of the eyes), dark urine, and pale-colored feces. Acute HCV usually resolves itself after 2-12 weeks, but can last as long as 26 weeks.

Chronic HCV

In a majority of people infected with HCV, the immune system does not completely clear the virus. The term "chronic hepatitis C" is used when HCV persists for more than six months. The percentage of HCV-infected people who develop chronic hepatitis C is typically estimated at 55% - 85%. Many people with chronic HCV do not have symptoms and lead relatively normal lives. Others may experience fatigue, nausea, indigestion, anorexia, fever, headaches, abdominal pain, and muscle and joint pain. Some people also develop mental symptoms, including depression, mood swings, or "brain fog" (mild confusion and forgetfulness). In a majority of people, HCV progresses slowly, but in 10-25% of chronically infected people, HCV progresses over the course of 10-40 years. Chronic HCV infection can lead to liver damage, including the development of fibrous tissue in the liver (fibrosis), fat deposits in the liver (steatosis), cirrhosis, and sometimes death.

Steatosis

Steatosis, also known as fatty liver, is a condition characterized by the accumulation of fat in the liver, and it is commonly seen in people infected with hepatitis C. It is estimated that between 30% and 40% of HCV positive individuals have steatosis, which is significantly higher than the 14% to 31% with steatosis in the general population. Steatosis has been found to increase the risk of HCV disease progression, reduce the likelihood of responding to HCV treatment, and may contribute to the development of liver cancer (hepatocellular carcinoma, or HCC).

The exact mechanism by which HCV increases the risk of steatosis in the liver is not well understood. Contributing factors that have been found to increase the incidence of

steatosis in the general population include type II diabetes (diabetes mellitus), hyperlipidemia (elevation of lipids or fats in the bloodstream), heavy alcohol consumption and a high body mass index (body weight relative to height). Most experts believe that there is an additional viral factor that increases the likelihood of HCV patients developing steatosis, but exactly what this is remains unclear.

On the other hand, it is clear that there is a direct viral mechanism involved in the development of steatosis in people infected with HCV genotype 3, even though this mechanism has not yet been determined. Studies show that most people with genotype 3 HCV have moderate to severe steatosis, regardless of any co-factors. Interestingly, patients with genotype 3 who achieve a viral cure or sustained virological response (SVR – continued undetectable HCV viral load six months after the completion of therapy) to HCV have a marked decrease and sometimes a complete resolution of steatosis, again regardless of any additional co-factors. This suggests that there is a relationship between steatosis development and HCV genotype 3. This is in stark contrast to patients with HCV genotypes other than 3, who show little improvement in the level of steatosis even after achieving an SVR.

In patients with HCV genotypes other than 3, co-factors such as high BMI, heavy alcohol intake, elevated blood lipids, glucose intolerance, and diabetes promote the development of steatosis. Since more patients with non-3 genotype develop steatosis than patients without HCV, experts believe that there is a synergy between steatosis, HCV of any genotype, and the other co-factors listed above.

There are no medications to treat steatosis. However, there are strategies to help reduce steatosis in people with hepatitis C and to lessen the impact of steatosis on HCV disease progression and treatment outcome. It appears that reducing heavy alcohol consumption, diet modification, exercise and maintaining a healthy weight are important strategies to help reduce or possibly eliminate steatosis in some people.

Cirrhosis

Cirrhosis is a process in which damaged or dead liver cells are replaced with scar tissue. About 10-25% of HCV-infected people develop cirrhosis after 10-30 years. Extensive scar tissue formation can interfere with the flow of blood through the liver, causing further cell death and loss of liver function. In people with compensated cirrhosis, the liver is heavily scarred but can still function relatively well; people with compensated cirrhosis may experience few or no symptoms. In people with decompensated cirrhosis, however, the liver cannot function properly; such people may experience a wide range of symptoms.

The obstruction of blood flow through the liver can lead to a condition called portal hypertension, or high blood pressure in the major blood vessels serving the liver. This, in turn, can lead to complications such as the development of varices, or stretched and weakened blood vessels in the esophagus, stomach, and gastrointestinal system. Sometimes varices burst and bleed; internal hemorrhage may cause vomiting of blood and tarry stools. If the liver is unable to synthesize sufficient albumin, fluid may accumulate in the abdominal cavity (a condition known as ascites) and the ankles and feet may swell (edema). Inadequate clotting factor production can lead to prolonged bleeding and easy bruising.

When the liver’s filtering ability is impaired, hormones, metabolic by-products, and other substances may accumulate in the body. Some people experience jaundice, dark urine, and pale-colored stools as bilirubin levels increase. The build-up of bile acids can cause pruritus (itching). An accumulation of estrogen can lead to spider angiomas (clusters of dilated blood vessels in the skin) and gynecomastia (breast enlargement in men). Toxic substances such as ammonia can affect the brain and cause hepatic encephalopathy, which may be characterized by cognitive dysfunction (problems with thinking), mental confusion, violent behavior, lack of concentration, lethargy, personality changes, dizziness, or hepatic coma. In the most severe cases, liver failure may occur. HCV is the leading reason for liver transplants in the U.S.

Symptoms Reported by People with HCV

Acute hepatitis C	Chronic hepatitis C	Late-stage hepatitis C with cirrhosis
Flu-like illness	Fatigue	Symptoms of acute and chronic hepatitis C (see columns 1 and 2)
Fatigue	Nausea	Internal bleeding
Nausea	Indigestion	Abdominal fluid accumulation (ascites)
Vomiting	Loss of appetite (anorexia)	Swelling of lower extremities (edema)
Diarrhea	Fever	Excessive bleeding and bruising
Indigestion	Headaches	Itching (pruritus)
Loss of appetite (anorexia)	Abdominal pain	Spider angiomas
Fever	Joint pain	Gynecomastia

Night sweats	Muscle pain	Cognitive dysfunction
Headaches	Mental depression	Mental confusion
Abdominal pain	Mood swings	Lethargy
Abdominal bloating	“Brain fog”	Personality changes
Joint pain (arthralgia)		Dizziness
Muscle pain (myalgia)		Peripheral vision problems
Jaundice		Weight loss (wasting)

Liver Cancer

Liver cancer may develop in people with late-stage chronic hepatitis C after the development of severe fibrosis or cirrhosis; this usually occurs after 25-30 years or more. The type of liver cancer seen most often in people with HCV is called primary hepatocellular carcinoma (HCC). An estimated 3-5% of people with chronic HCV will develop HCC, and liver cancer rates increase the longer a person has cirrhosis. HCC is more common in men and in people over age 50. Successful HCV treatment is thought to reduce the risk of developing HCC in patients with cirrhosis.

In HCC, abnormal liver cells grow out of control and form tumors. HCC is hard to detect at early stages because there are few specific symptoms. As a liver tumor develops, a person may experience pain in the upper right part of the abdomen or in the back around the right shoulder blade; however, many people with chronic HCV experience pain even without liver cancer. Sometimes a mass or lump can be felt from outside the body. Various tests are done to diagnose liver cancer and determine its stage. A chemical called alpha-fetoprotein (AFP) is often found in the blood of people with HCC and may act as a biological marker. Ultrasound, CT scans, MRI imaging, and X-rays may be used to detect liver tumors. Liver biopsy can reveal dysplastic (abnormal) or cancerous cells. HCC treatment methods include surgical removal of part of the liver (hepatic resection), percutaneous ethanol injection (PEI, a procedure in which ethanol is injected into the tumor), transcatheter arterial chemoembolization (TACE, injection of chemotherapeutic drugs into the tumor’s blood supply), systemic chemotherapy, cryosurgery (freezing), radiation therapy, and hyperthermia (heat therapy). In 2007 a medication called Nexavar was approved by the FDA to treat liver cancer. In clinical studies Nexavar improved overall survival rates without any serious adverse events.

Conditions Associated with HCV

A number of different extrahepatic (outside the liver) conditions have been associated

with HCV. Several of these are autoimmune conditions, in which the immune system attacks the body's own tissues. Autoimmune conditions are more common in women than men, and they are often associated with generalized fatigue and pain. Unfortunately, immunosuppressive drugs – the usual treatment for autoimmune conditions – may increase HCV replication. Among the many conditions sometimes seen in people with chronic HCV are cryoglobulinemia, glomerulonephritis, lichen planus, porphyria cutanea tarda, Sjögren's syndrome, scleroderma (hardening of the skin and connective tissue), fibromyalgia (muscle and joint pain accompanied by fatigue), certain types of arthritis, psoriasis (red, scaly patches on the skin), thyroid disease, blood cell deficiencies, vasculitis (blood vessel inflammation), heart and circulatory problems, insulin resistance, type 2 diabetes, and mental and psychological conditions. Most serious conditions occur in late-stage HCV disease after the liver has sustained extensive damage; some conditions have been linked to HCV treatment with interferon. A majority of people with HCV never experience serious associated conditions.

Cryoglobulinemia – a condition in which abnormal proteins called cryoglobulins form in the blood. When the blood is cooled, the cryoglobulins clump together, or precipitate. This causes the blood to thicken or “gel,” restricting the flow of blood (especially in the feet and hands). While as many as half of people with chronic HCV have evidence of cryoglobulins in their blood, most do not experience symptoms. Most experts believe that the presence of HCV itself somehow triggers the production of cryoglobulins. Because cryoglobulinemia can affect almost any part of the body, it can lead to a wide variety of symptoms. The most common are weakness, joint pain, and purpura (purplish blotches on the skin). Cryoglobulinemia can lead to blood vessel, nerve, skin, and tissue damage, especially in the extremities. Organs including the eyes, liver, kidneys, and spleen may also be affected. In some people, exposure to the cold makes symptoms worse. Cryoglobulinemia may be treated with nonsteroidal anti-inflammatory drugs, corticosteroids, or plasmapheresis (a procedure in which blood plasma is removed and filtered); however, in many cases, doctors recommend ongoing monitoring rather than treatment. Some studies have shown that HCV treatment can lessen the symptoms of cryoglobulinemia. Rituximab, a drug that has been approved to treat non-Hodgkin's lymphoma and rheumatoid arthritis, is currently under study as a treatment for hepatitis C-related cryoglobulinemia.

Glomerulonephritis – a disorder of the glomeruli, the small capillary beds in the kidneys where blood filtration takes place. The glomeruli become inflamed and damaged with scar tissue, and lose their ability to filter the blood. In people with HCV, membranoproliferative glomerulonephritis is often associated with cryoglobulinemia, in which cryo-

globulins build up in the kidneys. Symptoms of glomerulonephritis may include fatigue, high blood pressure, and edema, especially in the feet and ankles. Urine tests may reveal the presence of proteins such as albumin. Some studies suggest that treatment with interferon can reduce the rate of kidney disease progression, but with limited success. Other treatment options include plasmapheresis (removal of circulating cryoglobulins), and the use of corticosteroids. Studies are underway using interferon plus ribavirin (usually low dose), pegylated interferon with and without ribavirin, and Rituximab.

If glomerulonephritis persists for many years, the kidneys may fail (end-stage renal disease, or ESRD), necessitating a kidney transplant.

Lichen planus – an inflammatory disease that affects the skin and mucous membranes. Lichen planus is characterized by red or purple bumps, blotches, or blisters on the skin. Commonly affected areas include the wrists, ankles, neck, lower back, and genitals. Other manifestations of lichen planus include white patches or ulcers on the tongue, gums, or mucous membranes lining the mouth, and thin fingernails or toenails with ridges. Some people with lichen planus experience mild to severe itching or pain. Lichen planus may appear similar to several other conditions including bacterial or fungal infections; it is not, however, an infectious disease. While the cause of lichen planus is not known, some experts believe it is an autoimmune condition. There is no known cure for lichen planus, but various medications can reduce itching and improve and even clear lichen planus in some patients.

Porphyria cutanea tarda (PCT) – a condition in which porphyrins (by-products of hemoglobin production) build up to high levels in the body caused by a deficiency of an enzyme called uroporphyrinogen decarboxylase (UROD). This may be due to HCV infection; exposure to substances including alcohol, excessive iron, estrogen, or certain environmental toxins; or an inherited enzyme deficiency. In people with PCT, porphyrins accumulate in the liver and are transported to the skin, which becomes abnormally photosensitive (sensitive to light). PCT is diagnosed by measuring porphyrin levels in the urine and feces; if levels are high, urine may appear dark and reddish. Symptoms of PCT may include fragile skin, blisters, and discoloration in areas exposed to the sun; occasionally patches of skin may harden or become scarred. The usual treatment for PCT is phlebotomy, or blood removal, which reduces the amount of iron in the body. Treatment of the underlying cause (HCV) with interferon plus ribavirin has been found to decrease skin lesions as well as UROD's found in the urine. People with PCT sunburn easily, and should use sun-block and wear protective clothing.

Sjögren's syndrome – a chronic autoimmune disorder in which immune cells attack and damage moisture-secreting exocrine glands, including those that produce tears, saliva, and sweat. Symptoms include dry eyes, dry mouth and throat, and sometimes dry nose, dry skin, and vaginal dryness. Various organs – including the liver, kidneys, pancreas, lungs, thyroid, brain, nerves, and blood vessels – may also be affected, but this is uncommon. The exact cause of Sjögren's syndrome is not known, but it is often associated with other autoimmune conditions, such as rheumatoid arthritis and systemic lupus erythematosus. People with Sjögren's syndrome may experience mild or severe symptoms, which may be cyclical or progressive. Although there is no cure for Sjögren's syndrome, moisture replacement therapies (for example, artificial tears) may be helpful.

Arthritis – arthritis in general refers to inflammation of the joints. There are several different types of arthritis associated with HCV. Elevated levels of rheumatoid factor, a type of antibody that is present in people with RA (rheumatoid arthritis) is often found in people infected with HCV, but it is also common that in people with HCV there is an absence of true rheumatoid arthritis. Other types of arthritis seen in people with HCV include osteoarthritis (degenerative joint disease), reactive arthritis (Reiter's syndrome), and psoriatic arthritis. Symptoms of arthritis include pain, swelling, stiffness, and loss of function in the joints. Arthritis treatments include pain relievers and immunosuppressive drugs; heat therapy, cold therapy, and other measures can help manage pain. Some studies indicate that HCV treatment that succeeds in reducing viral load appears to improve HCV-related arthritis symptoms.

Thyroid disease – The thyroid is an endocrine gland in the neck that produces hormones that help regulate metabolism. Autoimmune thyroiditis is an inflammatory condition in which the immune system attacks the thyroid gland. Other thyroid conditions include hyperthyroidism (increased thyroid activity) and hypothyroidism (decreased thyroid activity). Some people develop thyroid disease while being treated with interferon; in most of these cases, thyroid function returns to normal once the drug is stopped. People with HCV– especially those who are receiving interferon treatment – should have their thyroid function tested regularly. Hyperthyroidism and hypothyroidism can both be treated; if a person's thyroid does not produce enough thyroid hormone, the hormone (T4) can be taken as a pill.

Blood cell deficiencies – Low levels of certain blood cells are present in some people with HCV. Low blood cell counts are caused by either inadequate blood cell production or excessive blood cell loss or destruction. Anemia (reduced ability of red blood cells to carry oxygen) may be caused by chronic disease or nutritional deficiencies. Neutropenia

(low levels of a type of immune system white blood cell) is often due to drugs that damage the bone marrow, where all blood cells are produced. Thrombocytopenia (a low level of platelets) may be an autoimmune condition or a result of drug toxicity or end stage liver disease (decompensated cirrhosis). In people with cirrhosis, portal hypertension can cause enlargement of the spleen; because the spleen is responsible for removing old blood cells from circulation, this can lead to the removal of an excessive number of cells. Drugs used to treat HCV may cause blood cell deficiencies. Ribavirin and HCV protease inhibitors are associated with hemolytic anemia, or red blood cell destruction. Interferon can decrease the production of white blood cells in the bone marrow. Various cytokines (substances produced by the body to stimulate blood cell production) can be used to treat blood cell deficiencies; these include erythropoietin (EPO), granulocyte colony-stimulating factor (G-CSF), and thrombopoietin (TPO).

Mental and psychological conditions – Mental conditions such as depression affect many people with HCV, and can occur as well as a side effect of HCV medications. Cognitive dysfunction, or problems with thinking, may be related to HCV disease itself or to its treatment. When the liver is badly damaged, it cannot properly filter out toxins such as ammonia, and these poisons can affect the brain. Cognitive dysfunction may include mental confusion, memory loss, inability to concentrate, difficulty processing information, and personality changes. Symptoms may range from mild to severe. Mild mental confusion, lack of concentration, and forgetfulness is sometimes referred to as “brain fog,” and may occur in HCV-positive people who do not have advanced liver disease. People with HCV may also experience psychological changes such as depression, anxiety, and mood swings. It is normal for people living with a chronic disease to feel somewhat anxious and depressed. However, severe or prolonged psychological changes may signal a physiological problem associated with liver disease. In addition, interferon causes depression, mania and anxiety as a side effect in some people.

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Version 10, October 2011
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