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Cambridge
Scholars
Publishing

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This book first published 2023

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-1762-4
ISBN (13): 978-1-5275-1762-2

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INTRODUCTION

1.1. Hepatitis C

1.1.1. Definition, etiology, pathogenesis and pathophysiology

Hepatitis C (previously known as "non-A, non-B hepatitis") is an inflammation of the liver caused by the hepatitis C virus (HCV). Hepatitis C virus is a worldwide problem. HCV was identified in the year 1989, whereas its genetic organization and protein products classified it in the Flaviviridae family [1]. HCV is not closely related to any of the other known hepatitis viruses. The HCV genome is a positive-sense RNA molecule. HCV is characterized by a high degree of genetic diversity. HCV contains 6 genotypes, 74 subgenotypes (subtypes) and an indefinite number of untypable HCV variants [2]. Its diversity of hepatitis C virus is particularly signficant not only in terms of HCV screening, diagnosis, disease progression and the patient's response to various HCV treatments, but also it prevents the development of vaccines, enabling the virus to rapidly evolve resistance to the defence mechanisms of the human body, consequently affecting the clinical outcomes in HCV-infected patients in terms of their poor response to the antiviral treatment of hepatitis C virus infection. The pathophysiology of hepatitis C infection involves several stages, which are similar to those of hepatitis B. When the HCV virus enters the body, it first infects the liver cells or hepatocytes, where it replicates and causes damage to the liver tissue. This damage triggers an inflammatory response by the immune system, which tries to clear the virus from the liver. However, in most cases, the immune response is not strong enough to completely clear the virus, and the infection becomes chronic. Over time, chronic hepatitis C infection can cause progressive liver damage, leading to liver fibrosis, cirrhosis, and ultimately, liver failure. In addition to liver damage, hepatitis C infection can also cause a variety of extrahepatic manifestations, such as cryoglobulinemia, lymphoma, and kidney disease, among others. These extrahepatic manifestations are thought to be due to the virus's ability to infect and

replicate in cells outside the liver. Hepatitis C virus (HCV) infection can cause kidney damage, although it is not a common complication of the disease. The exact mechanisms of kidney damage in HCV infection are not fully understood, but there are several ways in which the virus can affect the kidneys. One possible mechanism is through the formation of immune complexes in the kidney, which can lead to glomerulonephritis. This is an inflammatory condition that affects the tiny filters in the kidney, called glomeruli, leading to proteinuria (the presence of protein in the urine), hematuria (blood in the urine), and decreased kidney function. Another way that HCV infection can cause kidney damage is by directly infecting the kidney cells. HCV can replicate in a type of kidney cell called the renal tubular epithelial cell, leading to inflammation and damage to the kidney tissue. HCV infection can also increase the risk of developing other kidney diseases, such as membranoproliferative glomerulonephritis and IgA nephropathy. These conditions are characterized by inflammation and damage to the kidney tissue and can lead to proteinuria, hematuria, and decreased kidney function. Overall, while kidney damage is not a common complication of HCV infection, it can occur in some cases and should be monitored closely in individuals with hepatitis C.

1.1.2. Epidemiology

HCV is a significant public health problem in the whole world. Recent estimates from the World Health Organization (WHO) show that about 170-200 million people are infected with hepatitis C virus, which accounts for 3% of the world population. The prevalence of HCV infection varies worldwide, ranging from as low as 0.01% in Western Europe to up to 20% in Egypt. About 3 to 4 million people are reported to be newly infected with hepatitis C virus (HCV) per year [1]. Chronic HCV infection is currently considered to be the cause of the incidence of chronic liver disease (CLD) in the United States, with an estimated 8,000 to 10,000 deaths each year resulting from HCV-associated chronic liver disease [3]. Surveys conducted among the population of the Republic of Serbia indicated that about 1% (100,000) of the general population [1] was infected with hepatitis C virus (HCV), whereas there were no exact data obtained on the territory of Montenegro. The abovementioned surveys showed that HCV infection was found in healthcare workers (3%), injection drug users (over 50%) and patients on chronic hemodialysis (over 70%) as well. As regards the prevalence of HCV infection among hemodialysis patients, it was nearly 15%. A significant increase in the

incidence of HCV infection has been reported, which can primarily be explained due to a rapidly growing number of drug users in recent years [1]. Therefore, one should not be surprised to learn that chronic HCV infection has been estimated to cause approximately 300,000 deaths per year [2].

In the year of 2009, the number of patients undergoing a chronic hemodialysis (HD) programme was 191, out of whom 42 patients were HCV-positive which accounted for 21.9%. The largest percentage of HCV-positive patients was reported in Bijelo Polje (61.1%), Berane (50%), Rozaje (50%), Bar (25%), Kotor (18.7%), Herceg Novi (16.6%), Pljevlje (11.7%), Niksic (13.3%) and Podgorica (4.4%). The reason for such a high percentage of HCV positivity can be found in inadequate accommodation facilities used for the treatment of patients on hemodialysis (HD).

A man is always a source of hepatitis C virus infection, which can present as both acute or chronic HCV infection. The presence of the virus is indicated in almost all body fluids: blood, salive, urine, stool feces, semen, vaginal secretion and cervical mucus. However, the most common route of transmission of hepatitis C virus is parenteral, i.e., through direct exposure to infected blood and blood derivatives. After the routine serological testing of all donations for anti-HCV antibodies commenced in 1994 in our region, the transmission of this particular virus through blood transfusions and blood derivatives had no epidemiological significance [2]. Nowadays, injection drug users are at highest risk of acquiring HCV infection. The most common routes of transmission of hepatitis C virus are the following: the intravenous injection of illicit drug use (90%), sexual contact (0-6%), hemodialysis (10-20%), vertical transmission: mother-to-child transmission of HCV (2-7%), percutaneous exposure to infected blood (1%), accidental occupation-related injuries (ORIs) among healthcare workers (2%), nosocomial infections and infections after solid organ transplantation. The source of infection cannot be detected in 10-30% of patients [1, 35].

1.1.3. Clinical presentation

If the symptoms of hepatitis C occur in the first place, in those people who do develop symptoms, the average period from exposure to symptom onset ranges from two weeks to 6 months. Acute HCV infection is most commonly asymptomatic (a silent disease"), much rarely (15-20%) appears as a symptomatic disease (in an icteric form), whereas an

exceptionally rare form of the infection is fulminant hepatitis (FH) complicated by hepatocellular insufficency. However, after acute hepatitis resolves, the majority of patients (55-85%) are unable to fight off the virus, which may eventually lead to the development of chronic lifelong HCV infection [2]. The majority of aforementioned patients show no symptoms of the disease, and if they do develop any symptoms, the most common ones are the following: fever, fatigue, a moderate pain under the right rib cage, a loss of appetite, jaundice, nausea and vomiting, joint pain. The disease is most often accidentally detected after carrying out routine biochemical analyses or in case of voluntary blood donation. It is not rare either to establish a diagnosis of the disease at the end-stage of decompensated cirrhosis.

An important clinical feature of chronic HCV infection is the presence of a significant number of extrahepatic manifestations in HCV-infected patients, such as the following: essential mixed cryoglobulinemia (MC), type II and type III, membranoproliferative glomerulonephritis (MPGN), porphyria cutanea tarda (PCT), etc. Namely, the virus itself is shown to have tropism for bone marrow-derived stem cells and circulating monocytes, resulting in the development of circulating immune complexes (CICs) and their deposition on the endothelium of small vessels [2].

1.1.4. Complications and prognosis

After acute infection resolves, approximately 40% of patients make a full recovery, whereas about 60% of patients develop chronic infection. Around 20% of patients who develop a chronic or long term infection, progress to cirrhosis within 20-25 years, whereas hepatocellular carcinoma (HCC) occurs in approximately 20% of patients. Considering the oncogenic potential of the virus itself, it accounts for 60% of malignant liver tumors. The abovementioned complications are more common in patients on hemodialysis. Malnutrition is very common among hemodialysis patients along with the occurrence of other types of infections – inflammation processes and worsening of previously developed anemia as well [2, 4].

Hepatitis C represents a severe and common complication in patients on chronic hemodialysis. Serious health conditions of these patients result not only from severe and acute hepatitis C virus infection, but from the potential occurrence of chronic aggressive hepatitis, possibly progressing to cirrhosis with long-term cardiovascular complications followed by a complex hemodialysis procedure.

Patients on dialysis with hepatitis C may experience several complications, including:

1. Liver disease progression: Hepatitis C is a viral infection that affects the liver, and patients on dialysis with hepatitis C are at an increased risk of developing liver disease. This can lead to cirrhosis and liver failure, which may require a liver transplant.
2. Increased risk of infection: Patients on dialysis are already at a higher risk of infection due to their weakened immune system, and having hepatitis C can further increase this risk. This can lead to serious infections such as sepsis.
3. Cardiovascular disease: Patients on dialysis are already at an increased risk of cardiovascular disease, and hepatitis C infection can further increase that risk. This can lead to heart attacks, strokes, and other cardiovascular complications.
4. Hematologic complications: Hepatitis C infection can lead to various hematologic complications such as anemia, thrombocytopenia, and leukopenia, which can worsen the patient's overall health and require additional medical attention.
5. Increased mortality: Patients on dialysis with hepatitis C have a higher mortality rate compared to those without hepatitis C, mainly due to the increased risk of liver disease, infections, and cardiovascular complications.

It is important for patients on dialysis with hepatitis C to work closely with their healthcare team to monitor and manage these potential complications.

1.1.5. Prevention

During hemodialysis, a patient's blood is filtered through a machine to remove waste and excess fluid. The blood is then returned to the patient's body. If the machine or any of the equipment used in the treatment is contaminated with Hepatitis C virus, it can spread the infection to other patients.

This means that if a patient undergoing hemodialysis has Hepatitis C, their blood may be introduced into the dialysis machine, potentially contaminating the machine and putting other patients at risk.

To prevent the spread of Hepatitis C in hemodialysis units, strict infection control measures should be in place. This includes thoroughly cleaning and disinfecting all equipment between patients, using single-use

equipment whenever possible, and properly disposing of any materials that come into contact with a patient's blood. Patients with Hepatitis C should be separated from other patients during treatment and their blood should be handled with extra care.

It's important for healthcare providers and patients to be aware of the risks of Hepatitis C dissemination in hemodialysis and take steps to prevent the spread of the infection.

To prevent the dissemination of Hepatitis C through hemodialysis, several measures can be taken, including:

1. Strict adherence to infection control practices: Healthcare providers should follow strict infection control protocols and wear appropriate personal protective equipment, such as gloves and gowns, during patient care.
2. Use of dedicated equipment: Each patient undergoing hemodialysis should have dedicated equipment that is not shared with others. Disposable or single-use equipment should be used whenever possible.
3. Regular cleaning and disinfection: All equipment used during hemodialysis should be cleaned and disinfected thoroughly between uses. This includes the dialysis machine, tubing, and other accessories.
4. Patient screening: All patients should be screened for Hepatitis C before starting hemodialysis treatment. If a patient is found to be positive, they should be isolated from other patients during treatment and their blood should be handled with extra care.
5. Education and training: Healthcare providers and patients should be educated about Hepatitis C, its transmission, and ways to prevent its spread. Patients should be encouraged to report any signs of infection, and healthcare providers should be trained to recognize and respond to such reports promptly.

By following these measures, the risk of Hepatitis C dissemination through hemodialysis can be significantly reduced, protecting both patients and healthcare providers.

Screening for HCV infection in this population is critical to prevent the spread of the disease and to initiate early treatment.

The following steps can be taken to screen for hepatitis C positive patients on hemodialysis:

1. Obtain a thorough medical history: Obtain a complete medical history of the patient, including any risk factors for HCV infection, such as prior blood transfusions, intravenous drug use, and previous medical procedures.
2. Perform a serologic test: Perform a serologic test for HCV antibody on all patients with chronic kidney disease who are undergoing hemodialysis. The most common test is an enzyme immunoassay (EIA) for HCV antibodies. If the test is positive, it should be confirmed by a more specific test such as a recombinant immunoblot assay (RIBA) or nucleic acid testing (NAT) for HCV RNA.
3. Monitor liver function: Patients who test positive for HCV should have their liver function monitored regularly to detect any evidence of liver damage or disease.
4. Refer for treatment: Patients who test positive for HCV should be referred to a hepatologist or gastroenterologist for further evaluation and treatment. Treatment options include antiviral medications such as interferon and ribavirin.
5. Implement infection control measures: Strict infection control measures should be implemented to prevent the transmission of HCV in the hemodialysis unit. This includes using separate dialysis machines for HCV positive patients, disinfecting equipment and surfaces, and practicing proper hand hygiene.

In summary, screening for HCV infection in patients on hemodialysis involves obtaining a medical history, performing a serologic test for HCV antibodies, monitoring liver function, referring for treatment, and implementing infection control measures to prevent the spread of the disease.

Cleaning hemodialysis equipment is critical to prevent the transmission of hepatitis C virus (HCV) in the dialysis unit. Proper cleaning procedures must be followed to effectively eliminate HCV and other pathogens from the equipment. Here are the steps to properly clean hemodialysis equipment:

1. Wear personal protective equipment (PPE): Put on gloves, gown, mask, and eye protection before cleaning the equipment to protect yourself from exposure to bloodborne pathogens.

2. Disinfect surfaces: Disinfect all surfaces that come into contact with the patient or blood with a hospital-grade disinfectant. Pay special attention to high-touch surfaces, such as the dialysis machine, armrests, and patient chair.
3. Remove blood and other organic matter: Clean all surfaces with a detergent or enzymatic cleaner to remove blood and other organic matter before disinfecting.
4. Disinfect the dialysis machine: Use an EPA-registered disinfectant to clean the dialysis machine, including the internal components such as the dialyzer and bloodlines. Follow the manufacturer's instructions for disinfecting the machine.
5. Rinse and dry: Rinse all surfaces with water after disinfecting to remove any residual disinfectant. Allow the equipment to air dry completely before use.
6. Dispose of waste: Dispose of all contaminated materials, such as gloves, gowns, and cleaning supplies, in a biohazard bag or container according to the facility's protocol.

It is important to note that cleaning procedures may vary based on the specific equipment used and the facility's policies and procedures. Staff should receive regular training on proper cleaning and infection control procedures to ensure that they are following best practices to prevent the spread of HCV and other bloodborne pathogens.

Educating patients about Hepatitis C is an important step in preventing its dissemination through hemodialysis. Here are some ways healthcare providers can educate their patients:

1. Provide written materials: Provide patients with written materials about Hepatitis C and its transmission. This can include brochures, pamphlets, or fact sheets.
2. Use visual aids: Use diagrams or videos to show patients how Hepatitis C can spread through contaminated equipment or blood products.
3. Explain the risk factors: Explain to patients that having a history of injecting drugs or receiving blood transfusions prior to 1992 are the most common risk factors for Hepatitis C infection. Also, mention that people who received a blood transfusion or organ transplant prior to 1992 are at risk.
4. Describe the symptoms: Explain the common symptoms of Hepatitis C, including fatigue, nausea, abdominal pain, and jaundice.

5. Emphasize the importance of prevention: Emphasize to patients the importance of preventing the spread of Hepatitis C by following infection control practices, and to report any signs of infection promptly.
6. Encourage testing: Encourage patients to get tested for Hepatitis C, especially if they have any of the known risk factors.
7. Provide resources: Provide patients with resources where they can learn more about Hepatitis C, such as support groups or online resources.

By educating patients about Hepatitis C, healthcare providers can help prevent its spread through hemodialysis and improve the overall health outcomes of their patients.

1.1.6. Therapy

A high risk of fatal outcome along with reduced long-term survival rates were reported in HCV-infected hemodialysis patients. The implementation of peginterferon alpha (PEG-IFN-α) therapy turned out to be highly effective in terms of the suppression of hepatitis C virus and prevention of chronic progressive liver disease, as a result of which higher overall survival rates of patients were expected along with substantial improvements in health-related quality of life in the hemodialysis patient population [5].

Numerous approaches are used in the treatment of persons diagnosed with chronic hepatitis C virus infection, such as the following:

- antiviral treatment (HCV RNA positive)
- the use of hepatoprotective substances (selenium, silymarin, vitamin E, ursodeoxycholic acid)
- general measures (complete abstinence from all alcohol and other drugs) [1].

In HD patients with HCV, HCV infection usually takes a natural course, similar to the one it has in the general popuation. In patients with one or both kidney transplants, the course of HCV infection is accelerated with an increased virus replication and higher incidence of liver cirrhosis. Hence, an early administratiton of antiviral therapy in patients with chronic kidney insufficiency follows as the next logical step, taken for the purpose of reducing the prevalence of cirrhosis and its consequences. In addition,

therapeutic measures entail the utilization of other principles to optimize the treatment of HD patients: dialysis adequacy, anemia treatment, control of the levels of parathyroid hormone (PTH) along with malnutrition control [1, 5, 6].

The major goal of hepatitis C treatment is related to viral RNA elimination from the blood. All the current treatment protocols for the hepatitis C virus (HCV) infection are based on the utilization of various interferon alpha medications by giving injection into a muscle (intramuscular, IM) or by inserting the needle under the skin (subcutaneous, SC).

Interferon alpha is a naturally occurring glycoprotein secreted by host cells in response to virus infection. The role of the interferon (IFN) system is stimulating the induction of innate immune defences in response to virus infection. IFN treatment leads to successful virus elimination in 15% of patients diagnosed with chronic hepatitis C [7]. Pegylated interferon (PEG-IFN), which differs from interferon because it is a conjugate of IFN-α with polyethylene glycol, decreases the rate of interferon clearance from the body, which means that higher levels of the drug concentration are achieved by extending the dosing intervals. Higher treatment efficacy of hepatitis C virus infection with IFN-α is achieved by introducing daily oral ribavirin (RBV) [8, 9].

However, the treatment of hepatitis C virus infection with peginterferon alpha may harbour a heightened risk of the development of anemia and other types of infections, eventually leading to the need to increase the prescribed dose of erythropoietin (EPO) used for the therapy of HD patients diagnosed with anemia, which gradually increases the safety risks of both types of treatment, along with the treatment costs as well.

A high risk of fatal outcome along with reduced long-term survival rates were reported in HCV-infected patients receiving hemodialysis. The implementation of peginterferon alpha (PEG-IFN-α) therapy turned out to be highly effective in terms of the suppression of hepatitis C virus, reduction of complications and enhancement of survival rates in patients [9, 10, 11].

There is a multitude of factors influencing the success of therapy outcomes, such as the following: virus genotypes (GTs) – hepatitis C virus "subtypes", viral titer, age, the amount of ALT in the blood, histological finding – the degree of liver damage/fibrosis, race, body weight, gender, infection duration – the length of the incubation period, iron levels in the

blood, "interferon-naive" hepatitis C patients (who has not previously been treated with interferons), early virologic response (EVR). The effectiveness of pegylated interferon alpha-2a (PEG-IFN-α-2a) therapy demonstrated twice as good results compared to the ones obtained by applying interferon alpha-2a (IFN-α) therapy. The number of patients treated with pegylated interferon alpha-2a who reported to have achieved viral eradication in the blood during the therapy itself is 60-90%. Unfortunately, the recurrence of hepatitis C virus was reported during the treatment or after the treatment discontinuation in the cases of some patients who were initially showing positive response to therapy. Therefore, the overall success of therapy based on the use of a combination of pegylated interferon alfa-2a (PEG-IFN-α-2a) and ribavirin is approximately 50%. The use of ribavirin is contraindicated in HD patients due to their being more prone to developing ribavirin-induced hemolytic anemia (RIHA). According to some studies, the overall rates of sustained virologic response (SVR) are 56-61% (all genotypes), the harder-to-cure subgroup of patients' (genotype 1) SVR rates are 48-56%, whereas the easier-to-cure subgroup of patients' (genotype 2) SVR rates are 81-88% [1, 9, 10].

The most frequent adverse effects of the use of peginterferon alpha-2a in HD patients in combination with ribavirin, are the following: fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/agitation (33%), sleep disturbance (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), an allergic reaction at the site of the sting (23%), arthralgia (23%), depression (20%), pruritus (19%), dermatitis (16%) [11].

Simultaneous monitoring of HCV-infected hemodialysis patients treated with peginterferon alpha-2a or the implementation of conservative supportive therapy measures only – could indicate new findings regarding the overall benefit of using a modern therapeutic approach to the management of hepatitis C infection in HD patients. A specific problem that may arise in the treatment of hepatitis C virus infection with peginterferon alpha-2a, is reflected in a potentially reduced number of blood cell count which creates a need to closely monitor and regulate hemoglobin levels by introducing erythropoietin (EPO) therapy [12].

The treatment of hepatitis C virus infection with peginterferon alpha may harbour a heightened risk of the development of anemia and other types of infections (as a result of frequent neutropenia), eventually leading to the need to increase the prescribed dose of erythropoietin (EPO) used for the

therapy of HD patients diagnosed with anemia, which gradually increases the safety risks of both types of treatment, along with the treatment costs as well [13].

Besides treatment of hepatitis C virus infection with peginterferon alpha, Hepatitis C is also treated using direct-acting antiviral (DAA) drugs. There are 3 classes of currently recommended direct-acting antiviral (DAA) medications: NS3/4A protease inhibitors, NS5A polymerase inhibitors, NS5B polymerase inhibitors. Currently, it was shown that DAAs demonstrate good safety and efficacy in patients with renal impairment infected by Hepatitis C virus (HCV). In contrast, pegylated interferon-alpha (PEG IFN-α), the older regimen, had limited success.

Direct-acting antiviral (DAA) drugs are a newer class of medications used to treat hepatitis C. They work by targeting specific proteins involved in the replication of the hepatitis C virus, which helps to reduce the amount of virus in the body and prevent further damage to the liver.

DAA drugs are typically used in combination with other medications, such as ribavirin, to create a more effective treatment regimen. The specific combination of drugs used will depend on the genotype of the hepatitis C virus, as different genotypes may require different treatment approaches.

The duration of treatment with DAA drugs can vary depending on the severity of the infection and the individual's response to the medication. In many cases, treatment can be completed in as little as 8-12 weeks. However, in some cases, treatment may need to be continued for up to 24 weeks.

DAA drugs have been shown to be highly effective at treating hepatitis C, with cure rates of up to 95% in some cases. They also tend to have fewer side effects than older medications used to treat hepatitis C, such as interferon.

Some examples of DAA drugs used to treat hepatitis C include:

1. Sofosbuvir: This medication is typically used in combination with other medications, such as ledipasvir or velpatasvir. It is effective at treating most genotypes of the hepatitis C virus.
2. Ledipasvir/sofosbuvir: This combination medication is effective at treating genotype 1 of the hepatitis C virus, which is the most common genotype in the United States.

3. Velpatasvir/sofosbuvir: This combination medication is effective at treating all genotypes of the hepatitis C virus, making it a versatile treatment option.
4. Glecaprevir/pibrentasvir: This combination medication is effective at treating all genotypes of the hepatitis C virus and is typically used for patients who have not responded to previous treatment with other medications.

Overall, DAA drugs have revolutionized the treatment of hepatitis C, offering a more effective and tolerable treatment option for patients with this condition. With proper treatment, many patients are able to achieve a cure and prevent further damage to their liver.

Hepatitis C is a viral infection that can cause liver damage and other complications if left untreated. Pegylated interferon-alpha (Peg-IFN) and direct-acting antiviral (DAA) medications are two treatment options for hepatitis C, but they work in very different ways.

Peg-IFN is an older type of medication used to treat hepatitis C. It works by boosting the body's immune system to fight the hepatitis C virus. Peg-IFN is given as a subcutaneous injection once a week, and treatment usually lasts for 24-48 weeks, depending on the genotype of the virus and the individual's response to the medication. Peg-IFN is often used in combination with ribavirin, an antiviral medication that works by interfering with the replication of the hepatitis C virus.

DAA medications are a newer class of medications used to treat hepatitis C. They work by directly targeting specific proteins involved in the replication of the hepatitis C virus, which helps to reduce the amount of virus in the body and prevent further damage to the liver. DAA medications are typically taken orally, and treatment usually lasts for 8-12 weeks, although the specific duration of treatment may vary depending on the individual's genotype and response to the medication.

While direct-acting antiviral drugs (DAAs) have been shown to be highly effective in treating hepatitis C with cure rates of over 90%, like any medical treatment, they can also have some potential complications. However, the risks of complications associated with DAA treatment are generally considered to be low compared to the risks of not treating hepatitis C, which can lead to serious liver damage, cirrhosis, and liver cancer.

Some of the possible complications of DAA treatment for hepatitis C include:

1. Side effects: DAAs can cause side effects, although they are generally mild and temporary. Common side effects include fatigue, headache, nausea, diarrhea, and muscle aches.
2. Drug interactions: DAAs can interact with other medications, including prescription drugs, over-the-counter drugs, and herbal supplements. Patients should inform their healthcare providers of all medications and supplements they are taking before starting DAA treatment.
3. Drug resistance: Although rare, hepatitis C virus (HCV) can develop resistance to DAA treatment. This can occur if the patient has a strain of HCV that is not susceptible to the DAA being used, or if the patient does not adhere to the prescribed treatment regimen.
4. Liver injury: While uncommon, DAA treatment can cause liver injury in some patients, particularly those with advanced liver disease or cirrhosis.
5. Re-emergence of hepatitis C virus: Although rare, some patients may experience a relapse of hepatitis C after completing DAA treatment. This can occur if the virus was not completely eradicated during treatment or if the patient is re-infected with HCV.

It is important to note that the benefits of DAA treatment for hepatitis C generally far outweigh the risks of complications. DAA therapy has been shown to significantly reduce the risk of liver damage, cirrhosis, and liver cancer, and to improve overall health outcomes for patients with hepatitis C. Patients should discuss any concerns or potential complications with their healthcare provider before starting DAA treatment.

One of the main differences between Peg-IFN and DAA medications is their mechanism of action. Peg-IFN works by stimulating the body's immune system to fight the hepatitis C virus. This means that it can take several weeks or even months for the medication to become effective, as the body needs time to mount an immune response. In contrast, DAA medications work by directly targeting the virus, so they can rapidly reduce the amount of virus in the body and prevent further damage to the liver.

Another difference between Peg-IFN and DAA medications is their effectiveness. Peg-IFN is effective at treating hepatitis C, but its success

rate is overall lower than that of DAA medications. In clinical trials, Peg-IFN combined with ribavirin has been shown to cure approximately 50-80% of individuals with hepatitis C, depending on the genotype of the virus and other factors such as the individual's age and the extent of liver damage.

DAA medications, on the other hand, have a much higher success rate, with cure rates of up to 95% in some cases. The specific success rate of DAA medications can vary depending on the individual's genotype and other factors, but overall, they are much more effective than Peg-IFN.

A very important difference between Peg-IFN and DAA medications is their side effects. Peg-IFN can cause a range of side effects, including flu-like symptoms such as fever, chills, and muscle aches, as well as fatigue, depression, and irritability. These side effects can be severe, and many individuals are unable to tolerate the medication. Ribavirin can also cause side effects, such as anemia and fatigue.

DAA medications, on the other hand, tend to have fewer side effects than Peg-IFN. The most common side effects of DAA medications are fatigue, headache, and nausea, although these side effects are generally mild and temporary. Some DAA medications may also interact with other medications, so it is important for individuals to discuss their medications with their healthcare provider before starting treatment.

A final difference between Peg-IFN and DAA medications is their cost. Peg-IFN is an older medication and is generally less expensive than DAA medications. However, Peg-IFN requires regular injections and can cause severe side effects, which can increase the overall cost of treatment. DAA medications, while more expensive upfront, may ultimately be more cost-effective in the long term due to their higher success

The cost of treatment for hepatitis C with direct-acting antiviral (DAA) drugs can vary depending on a number of factors factors aswell, including the country or region where the treatment is being administered, the dosage and length of treatment, and whether it is used in combination with other medications.

In the United States, the cost of DAA treatment for hepatitis C can range from around $20,000 to $100,000 or more, depending on the medication and the length of treatment. The high cost of DAA drugs has been a source

of controversy, as it can limit access to treatment for many people who cannot afford it.

In other countries, the cost of DAA treatment for hepatitis C can be significantly lower due to government price negotiations, bulk purchasing agreements, or other factors. For example, in some countries in Europe, the cost of DAA treatment for hepatitis C is typically around $10,000 to $20,000, while in some low- and middle-income countries, the cost can be as low as a few hundred dollars.

In recent years, efforts have been made to increase access to DAA treatment for hepatitis C by reducing the cost of medications, increasing availability of generics, and negotiating lower prices through government or public-private partnerships. These efforts have helped to improve access to treatment for many people with hepatitis C, but challenges remain in ensuring that everyone who needs treatment can access it at an affordable cost.

The cost of treatment for hepatitis C with pegylated interferon-alpha (Peg-IFNα) can vary depending on a number of factors, including the country or region where the treatment is being administered, the dosage and length of treatment, and whether it is used in combination with other medications.

The cost of Peg-IFNα treatment for hepatitis C in other countries can be significantly lower due a number of factors that include government price negotiations or bulk purchasing agreements. For example, in many countries in Europe, the cost of Peg-IFNα treatment for hepatitis C is typically around $5,000 to $10,000, while in some low- and middle-income countries, the costs of treatment are significantly less and can be around a few hundered dollars.

It is important to note that Peg-IFNα is not commonly used as a first-line treatment for hepatitis C anymore, due to the development of newer and more effective medications such as direct-acting antiviral drugs (DAAs). Peg-IFNα is associated with more side effects and a lower success rate compared to DAAs. Therefore, DAAs are usually the preferred treatment for hepatitis C due to their higher cure rates and better side effect profiles.

In summary, the cost of treatment for hepatitis C with Peg-IFNα can vary depending on a number of factors, but it is typically more expensive than DAA therapy, and is not commonly used as a first-line treatment option.

1.2. Health care system in Montenegro

Montenegro is a country in Southeastern Europe in the Balkans. It's total population numbers roughly 621 000 citizens. The capital city of Montenegro is Podgorica. Podgorica is also the largest city in Montenegro and it is home to around 31% of the total population of Montenegro. It is also the city where the Clinical Center of Montenegro, nations only university hospital is located. Monenegro ranks as the 48th country in the Human Development Index, it is a member of the Unated Nations, NATO and the World Trade Organisation. The country is currently in the process of joining the Europian Union and its economy could be classified as the upper-middle-income economy. When it comes to the health care system in Montenegro, it is based on a social health insurance system. The healthcare system in Montenegro is a mixed system, with both public and private healthcare providers. The Ministry of Health is responsible for overseeing and regulating the healthcare system in Montenegro. This system provides coverage to the whole population of the country. Until recently it was mainly financed via social health care insurance. Now the health care system switched to a fully tax-funded health insurance system in 2022. Like it was previusly stated the population coverage is broad and it still includes all residents of Montenegro. However, out-of-pocket payments are high, accounting for 39% of current spending on health in 2019, and almost 10% of all households experienced catastrophic health spending in 2017. Finance aside, Montenegro has made progres in recent years in reducing unmet medical needs of its citizens. On the other hand, Montenegro suffers from high rates of antimicrobial medication consumption, high levels od tabaco and alcohol consumtion and other enviromental risk factors for chronic illnesses (relatively poor air quality in some parts of the country for example) [28]. Health care for citizens in Montenegro is provided at three levels: primary (health care centres), secondary (general and special hospitals) and tertiary (Clinical Centre of Montenegro). Hemodyalisis is provided on all levels of health care in Montenegro. At the primary level patients can acces their health care trough their primary care phisician. There are seventeen primary Health Care Centres in Montenegro: Primary Health Care Centre Andrijevica, Primary Health Care Centre Bar, Primary Health Care Centre Berane, Primary Health Care Centre Bijelo Polje, Primary Health Care Centre Budva, Primary Health Care Centre Cetinje, Primary Health Care Centre Danilovgrad, Primary Health Care Centre Herceg Novi , Primary Health Care Centre Kolašin, Primary Health Care Centre Kotor, Primary Health Care Centre Mojkovac, Primary Health Care Centre Nikšić, Primary

Health Care Centre Plav, Primary Health Care Centre Pljevlja, Primary Health Care Centre Podgorica, Primary Health Care Centre Tivat, Primary Health Care Centre Ulcinj. Health care at the secondary and tertiary level is provided in general and special hospitals and the Clinical Centre of Montenegro, through outpatient specialist consultations, as well as through hospital treatment in wards and through daily treatment of patients (day hospital). There are seven general hospitals in Montenegro: General Hospital "Blažo Orlandić" Bar, General Hospital Berane, General Hospital Bijelo Polje, General Hospital "Danilo I" Cetinje, General Hospital Kotor, General Hospital Nikšić, General Hospital Pljevlja. For the citizens of Podgorica, the capital city of Montenegro, Danilovgrad, Tuzi and Kolašin all secondary health care needs are met within Clinical Center of Montenegro. Clinical Center of Montenegro is also the only hospital operating on the tertiary level of health care in Montenegro. [28,29]

Public healthcare in Montenegro is provided by the Institute for Public Health, which is responsible for preventative healthcare, such as vaccinations, disease surveillance, and health promotion. *Additionally, there are four clinical centers in Montenegro, located in the cities of Podgorica, Niksic, Bar, and Berane, which provide specialized medical services, such as surgery, internal medicine, and pediatrics. There are also several general hospitals throughout the country, which provide a range of medical services (cio ovaj pasus bih makla iskreno).*

The public healthcare system is financed through a combination of government funding, social health insurance contributions, and patient co-payments. All residents of Montenegro are entitled to free healthcare services, although co-payments may be required for certain services, such as hospital stays or medications.

While the public healthcare system in Montenegro is generally adequate, there are some challenges and limitations. The system is underfunded, and there is a shortage of healthcare professionals in certain areas. Patients may experience long wait times for certain services or treatments, and there may be limited availability of certain medications or procedures.

Private healthcare in Montenegro is available for those who can afford it, and there are a number of private clinics and hospitals throughout the country. Private healthcare is not regulated by the Ministry of Health, but rather by the Montenegrin Chamber of Medicine, which sets standards for the quality of care provided by private healthcare providers.

In recent years, the healthcare system in Montenegro has undergone significant reforms aimed at improving the quality and efficiency of healthcare services. One of the major reforms has been the introduction of a family medicine system, which aims to provide more comprehensive and coordinated primary healthcare services to patients. Under this system, patients are assigned to a family doctor who is responsible for their overall healthcare needs, including preventative care, diagnosis, and treatment.

Another key reform has been the establishment of a national health insurance fund, which aims to improve the financial sustainability of the healthcare system. The fund is financed through mandatory contributions from employers, employees, and the government, and is used to cover the costs of healthcare services for all residents of Montenegro.

Despite these reforms, the healthcare system in Montenegro still faces a number of challenges. One of the main challenges is the shortage of healthcare professionals, particularly in rural areas. This shortage is due to a combination of factors, including low salaries, limited career opportunities, and the emigration of healthcare professionals to other countries.

An important challenge medical professionals are faced with is the limited availability of certain medical services and technologies, particularly in rural areas. This can result in long waiting times for certain procedures or the need for patients to travel to larger cities for treatment.

In conclusion, the healthcare system in Montenegro is a mixed system that provides free healthcare services to all residents of the country. Despite recent reforms aimed at improving the quality and efficiency of healthcare services, the system still faces a number of challenges, including a shortage of healthcare professionals and limited availability of certain medical services and technologies.

Overall, while there are some limitations to Montenegro's healthcare system, but the country has made significant progress in improving access to healthcare services in recent years, and continues to invest in the expansion and improvement of its healthcare infrastructure.

1.3. Hemodyalisis in Montenegro

When it comes to hemodyalisis in Montenegro, there are twelve hemodyalisis centers operating in the health care system of Montenegro.

The hemodyalisis centers are: hemodyalisis center Bar, hemodyalisis center Budva, hemodyalisis center Kotor, hemodyalisis center Tivat, hemodyalisis center Herceg Novi, hemodyalisis center Cetinje, hemodyalisis center Podgorica, hemodyalisis center Bijelo Polje, hemodyalisis center Plav, hemodyalisis center Rožaje, hemodyalisis center Berane, hemodyalisis center Pljevlja. Hemodyalisis centers located in Bar, Kotor, Berane, Pljevlja, Bijelo Polje all oparate on a secondary health care level while hemodyalisis is cunducted on a tertiary level in Clinical Center of Montenegro for the citizens of Podgorica, Kolašin, Tuzi and Danilovgrad.

The cost of hemodialysis treatment in Montenegro is covered by the National Health Insurance Fund for all citizens who are eligible for the fund. However, there may be some out-of-pocket expenses for patients who require additional medical services or equipment not covered by the fund.

There are also several patient support groups in Montenegro that provide information and resources to people with kidney disease and their families. These groups can be a valuable resource for patients who are undergoing hemodialysis treatment or considering starting treatment.

In Montenegro, people who are not eligible for hemodialysis treatment may have other options for managing their kidney disease. For example, peritoneal dialysis (PD) is a type of dialysis that can be done at home and may be an option for some people who are not eligible for or do not want hemodialysis.

Peritoneal dialysis involves using the lining of the abdominal cavity (the peritoneum) as a filter to remove waste products and excess fluid from the blood. The patient inserts a small tube called a catheter into their abdomen and fills the abdomen with a special solution that draws waste products and excess fluid out of the bloodstream and into the solution. After several hours, the solution is drained out of the abdomen and replaced with fresh solution.

Another option for managing kidney disease is conservative management, which involves managing symptoms and complications of kidney disease without dialysis or transplantation. This may include medications to control blood pressure and manage anemia, dietary changes to reduce the workload on the kidneys, and other supportive care measures.

It's important for people with kidney disease to work closely with their healthcare providers to determine the best treatment plan for their individual needs and preferences. Healthcare providers can provide information on all available treatment options and help patients make informed decisions about their care [28,29]

1.4. Chronic kidney disease

Chronic kidney disease (CKD) is a condition in which the kidneys gradually lose function over time. The kidneys are important organs that filter waste products and excess fluid from the blood, and produce hormones that regulate blood pressure and promote the production of red blood cells. When the kidneys are damaged or not functioning properly, waste products can build up in the bloodstream, which can cause a range of complications. [32]

CKD is often a progressive condition, meaning that it can worsen over time if left untreated. There are five stages of CKD, based on the level of kidney function, with stage 1 being the mildest form and stage 5 being the most severe.

Common causes of CKD include diabetes, high blood pressure, and other conditions that can damage the kidneys over time. Other risk factors for CKD include age, family history, and the use of certain medications.

Symptoms of CKD may not be apparent in the early stages of the condition, but as it progresses, individuals may experience fatigue, weakness, nausea, loss of appetite, and difficulty sleeping. They may also experience fluid retention, which can cause swelling in the legs and feet, as well as changes in urine output or appearance.

Diagnosis of CKD typically involves a combination of blood tests, urine tests, and imaging studies, such as a kidney biopsy or ultrasound. Treatment for CKD focuses on slowing the progression of the disease and managing symptoms, and may involve lifestyle changes, such as dietary modifications and regular exercise, as well as medications to manage blood pressure and control blood sugar levels. [32]

In some cases, CKD may progress to end-stage renal disease (ESRD), in which the kidneys are no longer able to function on their own. At this stage, individuals may require dialysis or a kidney transplant to replace the

function of the kidneys. Early detection and management of CKD can help to slow its progression and reduce the risk of complications.

1.4.1. Epidemiology

Chronic kidney disease (CKD) is a major public health issue worldwide, affecting millions of people. The epidemiology of CKD varies across different populations and regions of the world, but there are some common trends and risk factors that have been identified. [32]

Prevalence varies but it can be said that CKD affects about 10-15% of the adult population worldwide. In the United States, an estimated 37 million people have CKD, and millions more are at risk of developing it. CKD is more common among older adults, with the highest rates of prevalence seen among those over the age of 65. There are certain genetic and environmental factors that affect the prevalence of chronic kidney disease. Diabetes and hypertension are the most common underlying causes of CKD. Other risk factors for CKD include smoking, obesity, a family history of kidney disease, and a history of cardiovascular disease. Certain ethnic and racial groups are also at higher risk for CKD, including African Americans, Hispanics, and Native Americans.

The epidemiology of CKD highlights the need for continued efforts to prevent and manage this condition, particularly in populations at higher risk. Early detection and intervention, as well as effective management of underlying risk factors, can help to improve outcomes for individuals with CKD and reduce the burden of this condition on public health.

1.4.2. Pathophysiology

The pathophysiology of CKD involves a complex interplay of genetic, environmental, and lifestyle factors that can lead to kidney damage and dysfunction.

The most common causes of CKD are diabetes and hypertension, but other conditions and factors, such as glomerulonephritis, polycystic kidney disease, urinary tract obstruction, and prolonged use of certain medications, can also contribute to the development of CKD. [32]

There are several genetic conditions that can lead to the development of CKD, most notably: