HEPATITIS C

INTRODUCTION

Hepatitis C is a virus that causes a chronic infection of the liver. The hepatitis C virus was first identified in 1989. Since that time, hepatitis C has become a serious worldwide health issue. It has been estimated that approximately 170 million people are infected with hepatitis C. It is a significant cause of liver cancer, cirrhosis, and hepatitis, and as the population ages, it is expected that the number of people affected and the burden on the health care system will both increase. Improved screening techniques have significantly decreased the chances of hepatitis C being transmitted during blood transfusions. The majority of cases (in developed countries) are caused by IV drug use, and this is obviously a social issue that is very difficult to manage. There is no vaccine for hepatitis C, the available treatment is long, expensive, and risky, and the success rate for the therapy varies considerably depending on the form of the virus and other factors.

OBJECTIVES

When the student has finished this module, she/he will be able to:

1. Identify the correct definition of hepatitis C.
2. Identify the 2 most important clinical implications of hepatitis C infection.
3. Identify the type of virus that hepatitis C is considered to be.
4. Identify 3 characteristics of the virus that have treatment implications.
5. Identify the major route of transmission of hepatitis C in developed countries.
6. Identify the percentage of people with hepatitis C infection who will develop cirrhosis.
7. Identify the percentage of people with hepatitis C infection who will develop liver cancer.
8. Identify 3 relatively common complications of a hepatitis C infection.
9. Identify the 2 blood tests that are used to confirm the presence of hepatitis C.
10. Identify the “gold standard” test used to assess fibrosis and cirrhosis in patients with a hepatitis C infection.
11. Identify 2 other tests that can be used to detect fibrosis and cirrhosis.
12. Identify the most common genotype of hepatitis C in the United States.
13. Identify 2 factors that increase the risk of developing liver cancer.
14. Identify 3 patient characteristics that would indicate the need to screen for hepatitis C.
15. Identify a drug used to treat hepatitis C and its mode of action.
16. Identify a drug used to treat hepatitis C and its mode of action.
17. Identify the factor that most determines the success rate of the therapy for hepatitis C.
18. Identify the correct definition of sustained viral response.
19. Identify a serious, commonly experienced adverse effect of the therapy for hepatitis C.
20. Identify a commonly experienced psychological adverse effect of the therapy used to treat hepatitis C.
Epidemiology

Hepatitis C is the most common chronic, blood-borne disease in the United States. The Centers for Disease Control (CDC) has estimated that approximately 1.8% of the population of the United States has been exposed to hepatitis C, and of that number, 75% are viremic. Those numbers would mean that there are 2.7 million people with an active hepatitis C infection. Hepatitis C infections are the cause of approximately 20% of all cases of hepatitis and are responsible for 8000 to 10,000 deaths in the United States each year. Hepatitis C is also the most common cause of hepatic cancer (approximately 30% of all cases) and the leading indicator of a need for liver transplant.

Pathophysiology

Hepatitis C is caused by the hepatitis C virus. The hepatitis C virus is an RNA virus. RNA viruses (HIV, hepatitis C, Ebola, dengue, influenza, etc.) have very high replication rates, they are genetically very diverse, and they have a very high rate of mutation, a mutation rate that is several orders of magnitude greater than DNA-based viruses and organisms.

One of the reasons why RNA viruses mutate so intensely and are so genetically diverse is that these viruses have quasispecies. Quasispecies are variants of the virus with small – but very significant – molecular variations, and it is thought that quasispecies were developed by viruses as a survival tactic. By constantly producing new and different “profiles,” the virus can ensure its survival against the body’s immune system and drugs.

There are six major hepatitis C genotypes – genotypes 1 through 6 – and there are more than 100 subspecies. The most common genotype worldwide is type 1, and this is the most common genotype in the United States: approximately 72% of all patients in the United States with a hepatitis C virus infection have the type I genotype of the virus. Genotype 2 (an incidence of approximately 15%) and genotype 3 (an incidence of approximately 7%) are much less common in the United States. Genotypes 1a and 1b are very common in the United States.

Learning Break: Hepatitis C virus has six major genotypes, there are more than 100 subtypes of the virus, and it replicates and mutates very rapidly. These facts have enormous implications when clinicians are trying to eradicate the virus.

Transmission of Hepatitis C

The most common mode of transmission of hepatitis C is by exposure to infected blood. This happens most often – in developed countries – because of intravenous drug use. The CDC has estimated that 33% of people between the ages of 18-30 who use IV drugs are infected with hepatitis C, and the rate of infection is approximately 70% - 90% in older person who used, or still use IV drugs. IV drug use is by far the most risky behavior in terms of being infected with the hepatitis C virus; the rate of transmission of the virus is much higher than with any other mode of transmission.
Learning Break: Syringes used by people who are intravenous drug users have been tested, and the hepatitis C virus can persist in the syringe for many weeks, even when the syringe is subjected to relatively extreme temperatures.

There are other modes of transmission of hepatitis C. Most are uncommon, but some can be important in certain situations.

- Blood transfusion: Hepatitis C can also be spread by blood transfusion, but with greater awareness of the prevalence of the disease and better screening techniques of blood supplies, the risk of this is extremely low – perhaps 1 case of transmission for every 2 million transfusions.\(^{10,11}\)

- Hemodialysis: Patients who undergo maintenance hemodialysis have a much higher rate of hepatitis C infection than the general population, and these patients and the population of IV drug users account for the greatest number of hepatitis C infections in developed countries.\(^{12,13}\) The majority of the cases of hepatitis C infection associated with hemodialysis appear to be caused by poor technique and poor compliance with sterility precautions and protocols by dialysis unit personnel.\(^{14,15}\) Hepatitis C has been reported to be transmitted during medical procedures such as endoscopy, colonoscopy, etc., but the transmission rates in these situations are very low.

- Pregnancy: The hepatitis C virus can be transmitted from an infected mother to the fetus, but the rate of transmission is considered to be low, approximately 2% - 6%.\(^{16}\) If the viral load is high, the mother has an HIV infection, there are perineal lacerations during delivery, there is a prolonged rupture of the membrane, or an amniocentesis was performed, the risks are higher.\(^{17}\) The virus can be found in breast milk, but breastfeeding is not contraindicated.\(^{18}\)

- Sexual transmission: The information on sexual transmission of hepatitis C is confusing and contradictory. Hepatitis C can be detected in tears, semen, and saliva, but the rate of sexual transmission of the virus is thought to be very low. If both sexual partners are in a long-term, monogamous relationship, the risk of hepatitis C sexual transmission is thought to be approximately 0% - 0.6%, and the CDC does not recommend the use of barrier protection for these couples.\(^{19,20}\) One recent study that examined the medical literature concluded that there is no risk of sexual transmission of hepatitis if partners are in a monogamous relationship.\(^{21}\) However, if the infected partner or partners has used IV drugs, has had > 20 sexual partners, or if the couple engages in violent sexual activity, the risk of sexual transmission increases.\(^{22}\) There are reports of sexual transmission in which these and other risk factors are absent, but the rate of transmission is very low, and these cases may be due to unreported/under-reported IV drug use. Hepatitis C infections in men who have sex with men are common if the participants also have an HIV infection (hepatitis infection rates reported in this population to be approximately 9.4% to 17.8%),\(^{23,24}\) The incidence of hepatitis C infection among men who have sex with men but who do not have an HIV infection has been
reported to be equivalent to the incidence of the hepatitis C infection in the general population.\textsuperscript{25}

- Other forms of drug use: Insufflation of drugs (snorting) has identified as a route of transmission of hepatitis C.\textsuperscript{26}

- Family transmission: The risk of being infected with the hepatitis C virus is higher among people who are living with someone who has the virus then those who are not.\textsuperscript{27,28} The risk is not high, however, and these infections most likely happen when family members share toothbrushes, nail clippers, inhalants, etc., Hepatitis C cannot be contracted by sharing utensils, touching, coughing, sneezing, and other casual contact. It is not transmitted through insect bites, food, or water.

- HIV infection: The incidence of hepatitis C infection is much higher among men who have sex with men and who also have an HIV infection. This may be due to sex practices that increase the risk of exposure to contaminated blood, a higher rate of IV drug use among this population, or an unknown factor.\textsuperscript{29,30}

- Other causes: The risk of transmission of hepatitis C due to a needle stick is approximately 1.8\% - 3\%.\textsuperscript{31} In about 10\% of all cases of hepatitis C infection, no mode of transmission can be identified.\textsuperscript{32}

**NATURAL HISTORY OF HEPATITIS C INFECTION**

Hepatitis C causes inflammation and fibrosis of the liver. In approximately 15\% - 25\% of all people infected with the virus it is spontaneously cleared, although there is evidence that the spontaneous clearance rate can at times be as high as 50\%.\textsuperscript{33,34} However, it is clear from the published literature that most people infected with hepatitis C develop chronic hepatitis.

If the hepatitis virus is not spontaneously cleared, the natural history of those infected has been well documented.\textsuperscript{35} Approximately 80\% of those infected will develop a chronic, stable infection and it will not affect the person’s health. The other 20\% will develop cirrhosis and fibrosis; the extent of the cirrhosis and fibrosis depends on use of alcohol (more than three drinks/50 grams of alcohol a day) age, sex, obesity, presence of diabetes, and co-infection with other viruses. Most of these people -- 75\% - will have a clinical course that is slow and progressive, while the other 25\% will develop liver failure or liver cancer. This means that the risk of developing liver failure or liver cancer is approximately 1\% - 4\%.

**Learning Break:** The treatment for hepatitis C is takes 11 months, it is expensive, it causes numerous uncomfortable and potentially serious side effects, and for many patients there not a very good chance it will work. Most people with a hepatitis C infection will not die from the disease, but liver cancer is a grim diagnosis. It would be extremely useful to be able to predict who will develop liver failure and/or cancer so that those who will benefit from the treatment and those who won’t could be clearly
identified. This is not possible at this time, but if the patient with a hepatitis C infection abuses alcohol or uses IV drugs, has an HIV infection or a hepatitis B infection, has hemochromatosis (deposition of hemosiderin, an intracellular form of iron), developed the infection later in life, is male, has diabetes, or is infected with genotype 1B, there is a greater chance of developing liver cancer.\textsuperscript{36,37}

**DIAGNOSING HEPATITIS C**

Most patients with hepatitis C have chronic stable infections that do not affect their health and they have no signs or symptoms. People with cirrhosis can have fatigue, malaise, nausea, vomiting, peripheral edema, jaundice, and ascites. The liver transaminases may be normal (even if there are serious hepatic lesions) or they may be elevated, and they tend to fluctuate.

**Learning Break:** Because many people with a hepatitis C infection may not be aware they are carrying the virus, it is important that people who have a high risk of being infected are screened. This would include: people who do, or have used IV drugs, people with an HIV infection, people who received blood products or organ transplants before 1992, children born to a mother with a hepatitis C infection, people who received clotting factor products prior to 1987, and people who receive maintenance dialysis.

**Learning Break:** It is not recommended that the general population – i.e., people without specific risk factors for contracting hepatitis C – who are asymptomatic be screened for the virus.

The definitive tests that will confirm an infection with hepatitis C and let the clinician know what type and how widespread the infection are a) an **anti-HCV antibody screening** that detects antibodies against the core protein of the virus, b) if the anti-HCV test is positive, it is recommended to perform a **recombinant immunoblot assay (RIBA)** to confirm the infection, and c) viral load and viral genotyping.\textsuperscript{38} In certain circumstances (an early infection, or people who cannot make antibodies against the virus), the anti-HCV antibody test may be negative even if the person is infected, and a polymerase chain reaction (PCR) test for hepatitis C RNA should be obtained.

**Learning Break:** The RIBA test is recommended to confirm the diagnosis because in certain circumstances the test for anti-HCV antibody can yield a false positive.

**Learning Break:** Viral load actually measures hepatitis C virus RNA. The viral load fluctuates considerably over time, and an increase or decrease does not have any clinical significance. Also, the viral load is often referred to as “high” or “low,” and any measurement > 800,000 copies per IU/mL is considered high. However, a high viral load is not a completely reliable indicator that the patient will develop cirrhosis or cancer.

When an infection has been confirmed, an ultrasound examination of the liver is done to look for evidence of tumors, cysts, etc. Ultrasound has been shown to be useful for detecting early-stage liver cancer.\textsuperscript{39}
A liver biopsy can also be performed to assess the degree of inflammation and fibrosis. It can also help to discover and/or rule out other disease or pathologies. Unfortunately, it is possible that the tissue samples may not accurately represent the true extent of inflammation and fibrosis, and as with all such procedures, there can be errors by the pathologist. There are also complications (bleeding and infections), but these are very uncommon. At this time, although there is some controversy concerning its usefulness, liver biopsy is still considered to be the gold standard test for evaluation of the extent of fibrosis and cirrhosis in patients with a hepatitis C infection.

Other tests have been investigated for assessing liver inflammation and fibrosis in patients with hepatitis C. Transient elastography has been used as a non-invasive way of detecting the presence and/or extent of liver fibrosis. This technique uses an ultrasound that produces vibrations that “bounce” off the liver. By measuring the degree of rebound of these vibrations from the liver, elastography is able to determine how “stiff” the liver is which in turn reflects the degree of cirrhosis. It appears to be an accurate technique – and compares well with liver biopsy – for these purposes.

FibroTest (FT) is a measurement of five blood levels: alfa2-macroglobulin, apoliporoteinA1, haptoglobin, GTT, and bilirubin. It has been shown to compare favorably with liver biopsy for identifying cirrhosis and predicting five-year mortality. Another blood test that has been used to assess fibrosis is the Enhanced Liver Fibrosis (ELF) test. This is a combination of three markers of fibrosis: hyalauronic acid, amino-terminal propeptide-of-Type III collage, and tissue-inhibitor of matrix-metaloproteinase-1, and like the FibroTest it has been shown to be as effective (compared to liver biopsy) and it is probably superior (compared to transient elastography) for detecting liver fibrosis.

Learning Break: The blood components measured in the FibroTest and ELF are matrix components of liver cells, and various hepatic enzymes.

Liver fibrosis caused by hepatitis C is often staged in categories of 0/1 (no fibrosis or early fibrosis), 2 (intermediate), and 3/4 (advanced). Other rating scales exist (e.g., the Ishak scale, the Knodell histologic activity index) that measure the extent of the disease and the degree of fibrosis.

COMPLICATIONS OF HEPATITIS C

Aside from cirrhosis and liver cancer, there are many other complications that have been associated with hepatitis C infections. Some of these are clearly caused by the disease (e.g., cryoglobulinemia), others are strongly liked to hepatitis C (e.g., lichen planus), in some the associations with hepatitis C have been confirmed (e.g., diabetes mellitus), while for the association between the disease and hepatitis C gas been made only on the basis of anecdotal observations (e.g., rheumatoid arthritis).

- Diabetes: There is clinical and experimental evidence that indicates that an infection with the hepatitis C virus affects glucose metabolism and that patients infected with the hepatitis C have a higher incidence of type 2 diabetes than the general population. It appears that even after controlling for factors such as age,
obesity, etc., the presence of a hepatitis C infection is an independent factor that increases the risks for developing type 2 diabetes; in several studies this risk has been estimated to be two- to seven-fold.\(^5^1\)

**Learning Break:** Type 2 diabetes and insulin resistance appear to worsen the clinical progress of hepatitis C infections and reduce the effectiveness of therapy.\(^5^2,^5^3\)

- **Non-Hodgkin’s lymphoma:** Non-Hodgkin’s lymphoma has been reported in about 5% - 8% of all patients with a hepatitis C infection, and the risk of developing non-Hodgkin’s lymphoma may increase approximately threefold in patients with a hepatitis C infection.\(^5^4,^5^5\)

- **Dermatological complications:** Lichen planus is an inflammatory skin disease that is characterized by, pruritic, papular, scaly lesions. It has been suggested that lichen planus can be caused by hepatitis C, and there is evidence that the disease is much more common among people with a hepatitis C infection.\(^5^6,^5^7\) The signs and symptoms can be very annoying and irritating, but it is not a dangerous disease and does not cause serious or permanent harm. Porphyria cutanea tarda (PCT) is another skin disorder that has been strongly associated with hepatitis C infection. This disease is caused by reduced activity of a specific enzyme that is involved in the heme synthesis pathway.\(^5^8\) Porphyria cutanea tarda is manifested by photosensitive erythema, fragile skin, skin erosions, blisters, and scarring. The disease is very common among people with hepatitis C; one study estimated that approximately 50% of all patients with a chronic hepatitis infection had porphyria cutanea tarda.\(^5^9\) Infected skin lesions that heal slowly and scarring are common in patients with porphyria cutanea tarda.\(^6^0\) It has also been noted that patients with this disease are more likely than the general population to develop liver cancer, but this association has not been proven\(^6^1\)

- **Renal disease and hepatitis C:** Kidney disease has been associated with hepatitis C infection, and the most common type of renal disorder seen in patients with a hepatitis C infection is membranoproliferative glomerulonephritis (MPGN).\(^6^2,^6^3\) Membranoproliferative glomerulonephritis is a form of nephritis that is caused by a specific pattern of glomerular injury, and it can result in nephrotic syndrome, azotemia, and hematuria. The disease is a relatively common complication of hepatitis C: the incidence has been estimated to be approximately 40%.\(^6^4,^6^5\)

- **Cryoglobulinemia:** Cryoglobulinemia is the most common extrahepatic complication of hepatitis C infection.\(^6^6\) The disease is immune-mediated. It is characterized by deposition of immune complexes into the endothelium of small and medium-sized arteries and veins. This cause a widespread inflammation and vasculitis.\(^6^7\) The estimates of the prevalence of cryoglobulinemia in patients who have hepatitis C very considerably and range from 10% to 70%.\(^6^8\) The disease appears to be an independent factor that increases the risk of developing cirrhosis, and all of the hepatitis C genotypes are equally affected.
Thyroid disease: Thyroid disease is relatively common in patients with a hepatitis C infection. One author noticed a 13% incidence of thyroiditis in the patient population infected with hepatitis C; the incidence was 7% in the patients who were not infected with the virus. Antonelli et al found a much higher incidence (2% versus 0%) of thyroid cancer in patients with hepatitis C, and a higher incidence of hypothyroidism.

Pulmonary fibrosis: Pulmonary fibrosis is a complication of chronic hepatitis C infection. The approximate incidence of the disease in this patient population varies widely (0.04% to 13%) and there is some controversy as to whether there is a true cause and effect relationship.

Atherosclerosis: Some researchers have noted the presence of a hepatitis C infection increases the risks for developing coronary and carotid atherosclerosis.

Learning Break: The patient with a chronic hepatitis C infection has a heightened immune response, and this response to the infection appears to be the cause of the complications. There is evidence that strongly suggests that the type 2 diabetes, renal disease, thyroid disease, etc. are immune complex-associated diseases, i.e., autoimmune diseases.

The complications explained here are the most common ones and those for which there is either proof and/or very strong evidence for a cause and effect relationship. There have been case reports that have reported an association between hepatitis C and these diseases: psoriasis, chronic polyarthritis, rheumatoid arthritis, polyartheritis nodosa, Bechet’s syndrome, fibromyalgia, chronic urticaria, chronic pruritus, vitiglio, Kaposi’s pseudo-sarcoma, cardiomyopathies, corneal ulcer, erectile dysfunction, necrolytic acral erythema, peripheral and central neuropathies, and poly/dermatomyositis.

TREATMENT OF HEPATITIS C

There is no vaccine for hepatitis C so prevention of the disease is based on avoiding risk factors. In the event of an accidental exposure such as a needle stick, there is no solid evidence that treating with immune globulins or the standard hepatitis C protocol will prevent an acute infection from becoming chronic. (Remember: the risk of this occurring is very small).

Whether or not to treat a patient with chronic hepatitis C can be a difficult decision. Most people do not succumb to the disease, the duration of the therapy is long, the adverse effects are very unpleasant and at times dangerous, and there is no guarantee of a cure. However, most authorities recommend at least a trial of therapy for those patients who have a chronic infection, who have some evidence of fibrosis or cirrhosis, who have normal renal function, and who do not have a history of anemia or neutropenia. Once the decision has been made to treat the patient with a hepatitis C infection, the goal of
treatment is to try and eradicate the virus and by doing so, prevent the progression to severe liver damage and/or liver cancer.

Eradicating The Virus

The current standard treatment used to eradicate the hepatitis C virus is injections of interferon and oral ribavirin. Interferon (Pegasys® is a common brand name of the drug) is a synthetic version of interferon, a naturally occurring glycoprotein. Endogenous interferon performs many antiviral and immune functions, e.g., it stimulates the production of antiviral proteins that inhibit viral replication, enhancement of natural killer activity, etc. Synthetic interferon used to treat hepatitis C infections works by interfering with viral replication and function.80

The synthetic interferon that is used today comes in two forms: peginterferon-α-2a and peginterferon-α-2b. These drugs are pegylated: the interferon molecules have been attached to a molecule of polyethylene glycol (the peg). This formulation decreases the volume of distribution of the drug, increases the drug half-life, and reduces its clearance.81 Clinical evidence has clearly shown that because of these pharmacokinetic qualities, the pegylated interferons have significantly increased response to treatment compared to unmodified interferons when they are used as monotherapy or with ribavirin.82 The pegylated interferons are administered via injection, subcutaneously, once a week.

Learning Break: Although more research needs to be done, there is a lot of evidence that suggests that peginterferon-α-2A is more effective than peginterferon-α-2b.83

Ribavirin (Rebetol® and Copegus® are common brand names) is an oral medication that interferes with viral replication and modulates the body’s immune response.84 Ribavirin eradicates the hepatitis C virus and it also decreases liver inflammation caused by the infection. Combining pegylated interferon with ribavirin is a much more effective way to treat hepatitis C virus infections. When the two drugs are used together, the sustained virologic response (SVR; this will be explained later) is twice that of what can be attained using either drug alone.85 Ribavirin is an oral tablet, and the usual dose is 800 mg to 1200 mg a day, given in two doses.

The duration of the treatment with interferon and ribavirin depends on the patient’s genotype and response to therapy. Patients with genotype 1 and 4 are treated for 48 weeks. Patients with genotype 2 and 3 are treated for 24 weeks. In both groups, the response to therapy is evaluated several weeks after its start. If the hepatitis C RNA is undetectable or there has been a 2-log-fold decrease in RNA, the therapy should be continued for the full course. If there is no significant response, the treatment should be stopped as there is almost no chance it will be successful even if the full course is administered.86

The effectiveness of the interferon/ribavirin combination is variable and depends on patient factors (i.e., age < 40 is beneficial, presence/extent of cirrhosis, a low viral load, female gender, no use of alcohol, etc) but success of the therapy probably depends, for the most part, on the genotype. The genotypes 2 and 3 are much more treatable: the
The expected success rate for treating genotypes 1 and 4 is approximately 30% - 50% while the expected success rate for treating genotypes 2 and 3 is approximately 80%.\textsuperscript{87,88} Effectiveness of therapy is defined as SVR, and \textit{SVR is defined as absence of detectable hepatitis C RNA at the end of the treatment and at six months after the end of the treatment.}

\textbf{Learning Break:} Sustained viral response is not just a laboratory value. \textit{Attaining a SVR has been clearly shown to decrease the risk of developing liver cancer and reduce the mortality associated with hepatitis C.}\textsuperscript{89,90} There is also evidence that SVR is durable. Several studies noted a very high incidence of patients remaining virus-free for up to 7 years.\textsuperscript{91,92}

\textbf{Learning Break:} Some people who become infected with the hepatitis C virus do spontaneously clear it. However, researchers found that early treatment was associated with a higher rate of SVR, and they recommended that patients who contract the infection be treated quickly and aggressively. The longer the wait after the infection before treatment is started, the lower the rate of SVR.\textsuperscript{93}

Prior to treatment, serum blood urea nitrogen, serum creatinine, complete blood count, liver transaminases, serum glucose, and serum thyroid studies should be obtained. Patients should also be tested for the presence of HIV, hepatitis B and hepatitis A. Contraindications to interferon/ribavirin therapy include: sickle cell anemia, thalassemia major, pregnancy, breastfeeding, hepatitis, severe liver disease, and renal disease.

\textbf{Learning Break:} Renal function, bone marrow function, endocrine function, and liver function must be evaluated before starting therapy with interferon/ribavirin and during therapy with these drugs as both the disease and the treatment can affect the kidneys, bone marrow, the thyroid, and the liver.

The adverse effects of interferon/ribavirin therapy are numerous. The most common adverse effects cause significant discomfort, but they are not dangerous and will resolve once therapy has been stopped. However, there are some adverse effects associated with these drugs that have (rarely) serious consequences. Unfortunately, aside from these potentially serious adverse effects, the level of discomfort patients experience from these “minor” adverse effects is such that many stop therapy.

- \textbf{Minor adverse effects:} Arthralgias, fatigue, malaise, myalgias, fever, cough, itching, rash, diarrhea, pruritus, mouth ulcers, injection site pain, anorexia, nausea, emotional lability. Many of these are quite common and will affect up to 90% of all patients taking the therapy.\textsuperscript{94}

- \textbf{Major adverse effects:} Anemia, neutropenia, thrombocytopenia, significant depression, suicide, hypothyroidism, and retinopathy have been reported. The \textbf{hematological complications are relatively common:} up to 50% of patients treated with interferon/ribavirin will develop neutropenia, up to 48% will develop thrombocytopenia, and up to 34% will develop anemia.\textsuperscript{95} These effects are the
most reason (aside from the patient’s inability to tolerate the less serious adverse effects) that interferon/ribavirin therapy is stopped. Anemia, neutropenia, and thrombocytopenia can be managed with dose reductions or drugs that stimulate the bone marrow, and these values will return to normal once the interferon/ribavirin therapy has been stopped.96,97

Learning Break: Depression is a very common adverse effect caused by interferon/ribavirin: the incidence of depression has been reported to be as high as 66%.98 Suicidal ideation is common, but suicides are rare.99 Nonetheless, many patients taking interferon and ribavirin will need antidepressant medication and/or psychiatric counseling.100,101

HEPATITIS C AND THE PATIENT WHO IS HIV POISTIVE

Approximately 30% - 50% of people with an HIV infection are infected with hepatitis C.102 Patients with HIV and hepatitis C infection have a much higher risk of developing liver cancer, and these patients do not respond to interferon/ribavirin therapy nearly as well as the HIV-negative population with a hepatitis C infection.103 The response rate to interferon/ribavirin in patients infected with HIV is approximately ½ the response rate of the patients who are HIV-negative, and relapses after viral clearance are more frequent.104

NEW TREATMENTS FOR PATIENTS WTH HEPATITIS C

The success rate of the interferon and ribavirin treatment for hepatitis C genotype 1 – the most common genotype in the United States – is relatively low. However, the FDA has recently approved two drugs that have been shown to dramatically increase clearance of the hepatitis C virus.

These drugs – boceprevir and telaprevir – are direct acting antiviral agents. These drugs, when used with the standard interferon and ribavirin therapy, have been shown to produce a high rate of response in patients who have relapsed after standard therapy and patients who did not respond to standard therapy105 and a sustained virologic response of up to 75% has been reported.106

Boceprevir (brand name Victrelis™) and telaprevir (brand name Incivek™) are both protease inhibitors. Protease inhibitors prevent viral replication by inhibiting the activity of proteases. Proteases are enzymes that accelerate the cellular production of proteins that is induced by a virus when it enters a cell. Viruses need these proteins to replicate, and the protease inhibitors block activity of the protease enzyme.107 Boceprevir and telaprevir are prescribed as follows:

- The treatment protocol for boceprevir starts with four weeks of interferon and ribavirin therapy, then boceprevir is started. In patients who are treatment naïve, the viral load is checked 8 weeks from the start of the therapy. If the viral load is zero, all three drugs are continued until 24 weeks of therapy have been received, then the viral load is checked again If it is zero, therapy is stopped. If there is any detectable viral load during the period of 8 weeks to 24 week of therapy (the viral load will be checked at 8 weeks, 12 weeks and 24 weeks), all three drugs are
given until 36 weeks of therapy have been received. At that point the boceprevir is stopped but the interferon and ribavirin are continued until 48 weeks of therapy have been received. Patients who have previously been treated for hepatitis C and have a zero viral load between weeks 8 and 24 should receive all three drugs for 36 weeks; if the patient has a detectable viral load during the period of 8 weeks to 24 weeks of therapy, he/she should receive all three drugs for 36 weeks and then be treated with interferon and ribavirin until 48 weeks of therapy have been completed. Boceprevir is an oral medication, the dose is 800 mg, and it is taken three times a day with a light meal or snack.

**Learning Break:** Boceprevir has many of the side effects associated with interferon and ribavirin therapy. Anemia and neutropenia are very common, as are alopecia, arthralgia, chills, diarrhea, dizziness, fatigue, insomnia and nausea, etc. Dysgeusia (alteration in taste) is a common (incidence of approximately 32%) side effect of the drugs that is not caused by telaprevir. There are some drugs of several classes of commonly used medications (e.g., anticonvulsants and anti-tuberculars) that that should not be used in patients receiving boceprevir. Also, boceprevir is a strong inhibitor of the CYP34A/5 and the P-gp drug metabolizing enzymes, and there are many common drugs such as calcium channel blockers, digoxin, and warfarin that are primarily metabolized by these enzymes. Concurrent use of boceprevir and one of these drugs (See the Victrelis™ package insert for the complete list) could cause dangerously elevated plasma levels of digoxin etc. If a patient is receiving boceprevir, always check the boceprevir prescribing information before giving other medications.

- The dosing for telaprevir is 750 mg taken orally three times a day with food (not low-fat foods). In treatment-naïve patients or patients who have relapsed from previous therapy, telaprevir, interferon, and ribavirin are given for 12 weeks. The viral level is measured 4 weeks after therapy has been started and 12 weeks after therapy has been started. If the viral load is zero both times, the telaprevir is stopped and the interferon and ribavirin are continued for 12 more weeks. If there is a measurable viral level at week 4 or week 12, the telaprevir is stopped, and the interferon and ribavirin are continued for 36 more weeks. For patients who have been treated before and had no response or a partial response, telaprevir, interferon, and ribavirin are given for 12 weeks, the telaprevir is then stopped, and the interferon and ribavirin are continued for 36 more weeks.

**Learning Break:** Some of the common side effects of telaprevir are anemia, diarrhea, fatigue, pruritus, and rashes. As with boceprevir, telaprevir is a potent inhibitor of several drug metabolizing enzymes, the cytochrome P450 enzyme CYP3A and the P-gp enzyme, and the plasma level of commonly used drugs such as amiodarone, digoxin, and warfarin that (see the Incivek™ package insert for the complete list) that are primarily metabolized by these enzymes could become dangerous. If a patient is receiving telaprevir, always check the telaprevir prescribing information before giving other medications.

The sustained viral response rate of the respective drugs is similar. Anemia is more common as a side effect of boceprevir
LIVER TRANSPLANTATION AND HEPATITIS C

End-stage liver disease caused by hepatitis C is the most common indication for liver transplantation in Westernized countries. However, the results of liver transplantation for patients with hepatitis C are not very hopeful. The natural progression of hepatitis C, the progression of cirrhosis caused by hepatitis C, and the progression of decompensation to death are actually accelerated after liver transplantation: more than 40% of all patients infected with hepatitis who receive a liver transplant develop cirrhosis, and histologic features of a chronic carrier of hepatitis C are seen in 90%-95% of all patients within five years. These effects are rare if the organ recipient has cleared the hepatitis C virus prior to the transplant. In patients who still have circulating virus, the graft is infected during the transplantation procedure. Factors that increase the risk of liver failure, cirrhosis, etc. after liver transplantation include a) a high viral load in the serum and the liver, b) genotype 4 infection (possible but not confirmed), c) female gender, and d) host immune response.

NURSING CARE OF THE PATIENT WITH A HEPATITIS C INFECTION

Nursing care of the patient with hepatitis C should focus on patient education, emotional and psychosocial support, and monitoring the patient for adverse drug effects and the signs and symptoms of complications of the disease.

Patient Education

Patient education is a crucial part of caring for the patient with hepatitis C. The patient will need to have the information necessary for understanding and coping with a chronic, potentially serious illness. Specifically, the patient needs information about hepatitis C transmission, living with others (what behaviors are safe, what behaviors are not in terms of transmission), and self-monitoring for signs and symptoms of complications of hepatitis C. The patient will also need information about lifestyle issues (e.g., drug use, alcohol use, sexual activity) that can affect his/her illness. The patient should receive information, appropriate for his/her level of cognitive ability, about what the disease is and what it means to be infected with hepatitis C.

When the decision has been made to use the interferon/ribavirin therapy, the patient will need intensive support from the nurse because a great majority of these patients will be treating themselves at home. The patient will need to be taught sterile technique, injection technique, and the proper methods of disposing of hazardous material. The patient will need to understand that taking these drugs is a serious commitment; those patients with genotype 1 will need therapy for almost a year. He/she will need to understand that many of the adverse effects can be very unpleasant, but are not serious and can be managed with over-the-counter remedies or symptomatic care. But there are some adverse effects (e.g., neutropenia) that can have some very harmful consequences and require dosage adjustments or prescription drugs, and this must be stressed. The patient must also know that the therapy will require frequent doctor’s office visits and phlebotomies.
Emotional and Psychosocial Support

Having a disease such as hepatitis C is a frightening experience. There is a real risk of disability or death. The treatment protocol is very difficult and it is not guaranteed to work. Patients who are receiving the interferon/ribavirin must many times resign themselves to the fact that they will feel tired, weak, nauseated, etc. for almost a year. In addition, they will have to learn to treat themselves at home, and some patients find that a daunting task. These patients will obviously need a lot of emotional and psychosocial support. This support will help the patient cope with the illness and the adverse effects, but it also has a very practical benefit. Many patients who stop the interferon/ribavirin therapy protocol do so because they cannot tolerate the therapy. A skilled and knowledgeable nurse can help these patients with practical tips on how to cope with these adverse effects. The nurse can also offer emotional support. By being able to offer real-life solutions for coping physically and psychologically, the nurse can help the patient receiving the interferon/ribavirin therapy to “stay the course” and complete the treatment. The nurse may often be the first caregiver to notice the presence of depression in these patients, and can notify the physician and encourage the patient to seek help.

Monitoring for Adverse Drug Effects and Complications of the Disease

Monitoring for adverse drug effects and complications of the disease is not difficult. The nurse must be aware of the most common adverse drug effects and complications of the disease, know which ones are minor and which ones can be potentially serious, and be able to understand the difference between the two. For example, it is quite normal for a patient who is receiving interferon/ribavirin to feel fatigued. However, when fatigue progresses to a more serious lack of energy, it may indicate anemia and the physician should be notified. It is normal for the patient receiving interferon to have a cough and some dyspnea, but if the cough is productive and the dyspnea interferes with simple activities of daily living, these might be signs that indicate the presence of an infection and/or pulmonary fibrosis.
REFERENCES


82. Foster GR. Pegylated interferons for the treatment of chronic hepatitis C. *Drugs*. 2010;70:147-165.
111. Gane EJ. The natural history of recurrent hepatitis C and what influences this. *Liver Transplantation.* 2008;14:S36-S44.
112. Gane EJ. The natural history of recurrent hepatitis C and what influences this. *Liver Transplantation.* 2008;14:S36-S44.