BACKGROUND
Chronic hepatitis C (CHC) is a major public health problem and a leading cause of chronic liver disease globally including in our region, especially in Pakistan, where the prevalence of the virus is over 8%. Although the prevalence of hepatitis C virus (HCV) in Bangladesh and India is less than 1%, it represents a very large HCV reservoir, posing significant threat to the health and economy of these developing nations.

TRANSMISSION OF HEPATITIS C VIRUS
Hepatitis C virus is primarily transmitted through infected blood or blood products. Injectable drug abuse remains an important mode of transmission of the virus including in the United States. Other potential
sources of HCV transmission include exposure to infected blood and sexual exposure. Sharing of razor, toothbrush, etc. also can lead to HCV transmission. The virus is not transmitted by hugging and sharing of eating utensils, dresses, or toilets. Patients with hemophilia and those on renal dialysis should be tested for HCV. Other situations that deserve to be considered include traditional medical practices like acupuncture, body piercing, tattooing, and commercial barbering.

**NATURAL HISTORY OF HEPATITIS C VIRUS INFECTION**

Fifteen percent to forty-five percent patients with acute hepatitis C do not recover and develop CHC. Of them, up to 20% go on to develop liver cirrhosis over a period of 15–20 years, whereas 30% HCV cirrhotics develop end-stage liver disease within 10 years and hepatocellular carcinoma (HCC) at a rate of 1%–2% annually.

**LABORATORY TESTING FOR HEPATITIS C VIRUS INFECTION**

It is customary to test a person initially for antibodies to HCV (anti-HCV) and then to detect HCV RNA by PCR. A negative HCV RNA test in a person, who is positive for anti-HCV, suggests resolved infection. However, the test may be false negative and rarely the patient may have low viremia. If an anti-HCV positive person tests negative for HCV RNA by PCR on two occasions, no further HCV testing is needed.

However, there are instances when a negative anti-HCV does not exclude active HCV infection. For example, acute HCV infection or immunosuppressed states like diabetes mellitus, patients on hemodialysis, and those receiving anticancer chemotherapy.

HCV RNA becomes detectable by PCR within 1 to 2 weeks, whereas it takes at least 8 weeks post exposure for anti-HCV to become positive.
There are six major HCV genotypes\textsuperscript{3} that determine treatment response and duration of infection,\textsuperscript{4} but not the disease outcome. Genotyping can be done either by reverse hybridization or by restriction fragment length polymorphism. The commercially available tests cannot identify HCV genotype in approximately 3% cases,\textsuperscript{5} while 1%–4% patients may have HCV infection mixed genotypes.\textsuperscript{6}

### LIVER BIOPSY IN CHRONIC HEPATITIS C

Unlike in the initial days of HCV treatment, when the response was not so exciting, liver biopsy today is perhaps no more mandatory in managing CHC patients, especially when the patients pay for their treatment from own pockets, as is the case in our region.

Liver biopsy provides useful information about the stage of hepatic fibrosis and grade of hepatic necro-inflammation; thus, remaining important in terms of predicting the prognosis in CHC patients.\textsuperscript{7} The scoring system that is widely used in Bangladesh is the Knodell–Ishak system.\textsuperscript{8}

It has been suggested that patients with milder hepatic fibrosis show better treatment response.\textsuperscript{9} Liver biopsy is also useful in monitoring disease progression. A 4–5 year interval is usually recommended between two successive biopsies.\textsuperscript{10}

### TREATMENT OF CHRONIC HEPATITIS C

The goal is obviously to eradicate the virus as well as to prevent complications. HCV is considered to have been eradicated when HCV RNA in serum remains undetectable at the end of treatment and 6 months later by PCR. This is called sustained virologic response (SVR). Improvement in hepatic histology has been observed in patients who achieve SVR with pegylated interferon in combination with ribavirin.\textsuperscript{11}
Currently, the recommended treatment for CHC is weekly subcutaneous injections of long-acting peginterferon in combination with oral ribavirin. Peginterferon is produced by binding polyethylene glycol moiety to interferon. This decreases renal clearance of the drug, thus altering its metabolism and increasing half life.\(^1\)

Response to peginterferon plus ribavirin depends on HCV genotype and pretreatment HCV RNA level. Genotype is the strongest predictor of response, and SVR is highest in patients with genotype 2 or 3 HCV infection. The response rate is 76\%–82\% in genotypes 2 and 3, compared to only 42\%–46\% in genotype 1. Lower pretreatment HCV RNA, younger age, lower body weight, and absence of significant hepatic fibrosis are other helpful parameters.\(^4\)

At least a 2 log decline of HCV RNA from baseline at week 12 on treatment is defined as early virologic response (EVR), and 65\% of patients with EVR subsequently go on to achieve SVR. On the contrary, 97\% of those who do not attain EVR, fail to develop SVR.

Multicenter, randomized, controlled trials have established the optimal dose of peginterferon \(\alpha\)-2a at 180 \(\mu\)g and that of ribavirin at 800–1000 mg daily for 24–48 weeks depending on HCV genotype.\(^13\)

Side effects of peginterferon-\(\alpha\) include neutropenia, thrombocytopenia, “flu-like” symptoms, depression, hypothyroidism/hyperthyroidism, irritability, loss of concentration and memory disturbances, visual disturbances, fatigue, muscle aches, headaches, nausea and vomiting, skin irritation, low-grade fever, weight loss, insomnia, hearing loss, and hair thinning.\(^14\) The complications typically associated with ribavirin are hemolytic anemia, fatigue, itching, rash, sinusitis, birth defects, and gout. Because of the teratogenicity of ribavirin, it is important that patients who receive ribavirin do not conceive for at least 6 months post-treatment.
Erythropoetin and granulocyte colony-stimulating factor (G-CSF) can be used to correct anemia and neutrophilia, respectively. “Flu-like” symptoms tend to be more severe in the initial weeks and can be managed with acetaminophen.

Therapy is contraindicated in patients with uncontrolled depressive illness; kidney, heart, or lung transplantation recipients; patients with co-existent autoimmune hepatitis or other conditions that are exacerbated by interferon and ribavirin; untreated hyperthyroidism; pregnant women; those with severe comorbidities (e.g., severe hypertension, heart failure, significant coronary artery disease, poorly controlled diabetes, obstructive pulmonary disease), those under 3 years of age; and individuals with known hypersensitivity to anti-HCV drugs.

Anti-HCV therapy is widely accepted in anti-HCV RNA positive patient not less than 18 years of age with abnormal ALT values, liver biopsy showing significant hepatic necro-inflammation and/or fibrosis, compensated liver disease with no evidence of hepatic encephalopathy or ascites. Treatment is absolutely contraindicated in those with decompensation of liver.

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Treating non-responders and partial responders to anti-HCV treatment remains a challenge. Retreatment with peginterferon-α and ribavirin achieves SVR in 25%–40% partial responders and in about 10% nonresponders. However, the duration of treatment has to be extended by 12–24 weeks depending on HCV genotype. Factors predicting better chances of response to re-treatment include HCV genotype non-1, lower baseline HCV RNA, less severe hepatic fibrosis, and Caucasian race.
Relapsers i.e., patients who relapse after an initial response, usually achieve SVR on re-treatment for longer duration. As expected, genotype 2 and 3 and low HCV RNA predict favorable outcome.

There is an emerging school of thought supporting maintenance of anti-HCV treatment in order to slow down, if not prevent, the progression of hepatic fibrosis and thereby delaying cirrhosis and HCC and even reversing early cirrhosis.  

There are certain other special scenarios in CHC management that deserve special attention. One is treating HCV-infected children. In the United States, an estimated 240,000 children are HCV infected. Children at risk for HCV infection include those born to HCV-infected mothers and those who received unscreened blood or blood products. Unlike adults, children are less likely to develop symptoms and more likely to clear the virus spontaneously. Interferon is FDA approved in children over 3 years of age, and interferon together with ribavirin is recommended for treating HCV-infected children. SVR is achieved in 25% genotype 1 and up to 70% non-1 genotype infected children. Fortunately, side effects are also uncommon in children. In fact, children appear to tolerate interferon better than adults.

Hepatitis C virus–infected mothers do not need to avoid breastfeeding. Both vertical and early horizontal transmission of HCV is rare.

In the west, approximately 10%–25% HIV-infected persons are co-infected with HCV. Progression of liver disease is more rapid in HIV-HCV co-infected persons. They run a 2-fold increased risk of developing liver cirrhosis. The likelihood of achieving SVR is lower in HIV-HCV co-infected persons. Although there is no FDA-approved medication for treating HIV-HCV co-infection, peginterferon-α plus ribavirin is widely used. However, the optimal dose and duration of anti-HCV therapy differs from those who do not...
have HIV co-infection. Most authors recommend treatment for longer duration. However, if any patient is receiving anti-HIV drugs like zidovudine, zalcitabine, and stavudine, careful monitoring is recommended as ribavirin may antagonize these drugs.

Hepatitis C virus infection has been associated with cryoglobulinemia that can lead to membrano-proliferative glomerulonephritis. Hepatitis C virus infection has been associated with cryoglobulinemia that can lead to membrano-proliferative glomerulonephritis. Kidney disease patients run an increased risk of acquiring HCV through blood transfusions, exposure to HCV-contaminated equipment during hemodialysis and rarely at the time of renal transplantation. Prevalence of HCV infection in hemodialysis recipients vary between 5% and 50%.

The goal of treating patients on dialysis as well as those with less severe degrees of renal impairment is to reduce progression of liver disease and/or to clear hepatitis C virus infection in those who might later need to undergo renal transplantation. Prevalence of HCV infection in hemodialysis recipients vary between 5% and 50%.

The goal of treating patients on dialysis as well as those with less severe degrees of renal impairment is to reduce progression of liver disease and/or to clear hepatitis C virus infection in those who might later need to undergo renal transplantation. However, use of ribavirin is not recommended, because the drug is not removed during dialysis and its accumulation leads to hemolytic anemia. The dose of peginterferon-α must also be adjusted depending on creatinine clearance rate.

In the course of CHC, progression of fibrosis varies. It depends on certain cofactors. In this context, the focus is on insulin resistance. Insulin resistance occurring in CHC induces fatty change in the liver and contributes to the progression towards cirrhosis and at the same time decreasing the chance of SVR.

There are some reports in the literature about the beneficial effects of ursodeoxycholic acid (UDCA) in treating HCV infection. A study involving over 100 patients demonstrated that interferon in combination with UDCA yields better response with sustained response in 8%. An earlier report by another Italian group also demonstrated normalization of ALT as well as better response in interferon plus
UDCA treated CHC patients compared to those treated with interferon.\textsuperscript{28}

Recent data show that more than the genotype it is rapid viral response (RVR) that will determine the possibility of sustained viral response. Rapid viral response is defined as negative HCV RNA after 4 weeks of treatment. The chances of SVR, if RVR is achieved, are more than 90\% irrespective of the genotype. If possible, the dose of ribavarin should be maintained to at least 60\% of the ideal dose in case of ribavarin associated side effects for the first 20 weeks to have an SVR.

Data on prevalence of HCV infection in India are still emerging. In a study from the All India Institute of Medical Sciences, Delhi, an enzyme immunoassay (EIA) was developed in-house for the detection of anti-HCV antibody against the prevailing genotypes in India. The specific reactivity of the test was compared with commercial second- and third-generation EIAs and reverse transcription nested polymerase chain reaction (RT-nested PCR). Fifteen thousand nine hundred twenty-two healthy blood donors were screened. Two hundred ninety-five (1.85\%) of these donors were positive. The screening was also used to determine how many patients with acute hepatitis and chronic liver diseases were positive for anti-HCV antibody. Five hundred sixty-four chronic liver disease patients were screened for anti-HCV antibody and 78 (13.83\%) were found positive. Two hundred forty-seven sporadic acute viral hepatitis patients were screened for viral infection markers. Hepatitis B and E viruses (HBV and HEV) were the major etiologic agents. HCV was associated with 9\% of the acute cases. Anti-HCV core IgM with HCV RNA detection was found to be helpful for the diagnosis of acute HCV infection.\textsuperscript{29}

**CONCLUSION**

Hepatitis C virus is a menace that burdens both sides of the globe, and the issue of treating chronic hepatitis C is an ever evolving one with large number of clinical trials ongoing at different centers.

**REFERENCES**


CASE STUDY 1

History

The first patient was a young 34-year-old gentleman who was incidentally diagnosed with HCV infection during voluntary blood donation. He had no history of blood transfusion, undergoing surgery or dental procedure, and injectable-drug abuse. He, however, frequently visited barbershops for shaving and haircut.

Clinical Examination

He had no complaints; on physical examination, there were no stigmata of cirrhosis.

Investigations

His investigations revealed HCV RNA load of $1.2 \times 10^4$ copies/mL. Genotype was 3, subtype b. His serum ALT was 96 U/L, serum albumin 38 mg/dL, prothrombin time 14 seconds (control 12 seconds). He tested negative for HBsAg. Abdominal ultrasonography and endoscopy of upper GI tract were both normal.

Diagnosis

The patient was diagnosed as a case of CHC.
Management

The patient was treated with injection peg-interferon $\alpha$-2a (180 $\mu$g) subcutaneously once weekly plus capsule ribavirin (200 mg) twice daily for 24 weeks. The course of treatment was uneventful with only occasional complaints of nausea and malaise.

Outcome

The patient attained HCV RNA negativity at 4 weeks (rapid virologic response [RVR]), 12 weeks (early virologic response [EVR]), 24 weeks (end of treatment response [ETR]), and also at 24 weeks (sustained virologic response [SVR]) post-treatment. The patient was fortunate that he could afford the treatment and also achieved the desired response.

CASE STUDY 2

History

The second patient was a 54-year-old middle-aged lady. She was detected to be anti-HCV positive at routine health checkup and had history of emergency surgery following a road accident.

Clinical Examination

Her physical examination was normal.

Investigations

Her baseline HCV RNA was $4 \times 10^8$ copies/mL and ALT 42 U/L. Liver cirrhosis was excluded. There was no HBV co-infection.

Diagnosis

Her diagnosis was also CHC.

Management

She also received treatment with injection peginterferon-$\alpha$ (180 $\mu$g) subcutaneously once weekly plus capsule ribavirin (200 mg)
twice daily for 24 weeks. She required additional erythropoetin and G-CSF injections on several occasions during the course of her treatment for anemia and leukopenia, but no dose reduction was done at any stage.

Outcome

Although the patient attained RVR, EVR, and ETR, her HCV RNA tested positive at 24 weeks post-treatment. She was treated again with the same regimen for another 36 weeks, but this time tablet metformin (250 mg) twice daily was added as her insulin resistance was found to be 2.5. The patient did achieve SVR at this occasion.

CASE STUDY 3

History

The third patient was a 38-year-old businessman with history of kidney dialysis in Thailand following which he tested positive for anti-HCV by ELISA. The patient was negative for HCV before undergoing dialysis.

Clinical Examination

He had no significant finding on clinical examination.

Investigations

His ALT was 34 U/L. Ultrasonography of whole abdomen as well as endoscopy of upper GI tract were both normal. On further evaluation, his HCV RNA was $4.11 \times 10^5$ copies/mL; when HCV genotyping was done, it was found that he was infected with mixed HCV genotypes 5 and 6. HBV co-infection was excluded.

Diagnosis

Our diagnosis in this case was CHC.

Management

We decided to treat the patient with peginterferon-α 135 µg once
weekly for 12 months. We did not give him cap. ribavirin since he was a diagnosed case of chronic renal failure with low creatinine clearance rate.

**Outcome**

The patient tolerated the treatment well. He showed SVR at 6 months post–treatment.¹

**Reference**