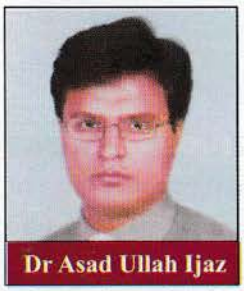
# Treating Hepatitis C in Primary Care Settings

## PAFP (Regd) Guidelines for the management of Hepatitis C



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The hepatitis C virus (HCV) is one of the most important causes of chronic liver disease in the Pakistan. It accounts for about 70 percent of liver related admissions in a medical ward including cirrhosis, end-stage liver disease, and liver cancer. Of the Pakistani population, nearly 8% percent have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. In this article we will focus on how to diagnose, manage, and treat a person having hepatitis C.

### Clinical Symptoms and Signs

Many people with chronic hepatitis C have no symptoms of liver disease. If symptoms are present,

They are usually mild, nonspecific, and intermittent. They may include

- fatigue
- mild right-upper-quadrant discomfort or tenderness ("liver pain")
- nausea
- poor appetite
- muscle and joint pains

Similarly, the physical exam is likely to be normal or show only mild enlargement of the liver or tenderness. Some patients have vascular spiders or palmar erythema.

### Clinical Features of Cirrhosis

Once a patient develops cirrhosis or if the patient has severe disease, symptoms and signs are more prominent. In addition to fatigue, the patient may complain of muscle weakness, poor appetite, nausea, weight loss, itching, dark urine, fluid retention, and abdominal swelling.

Physical findings of cirrhosis may include

- enlarged liver
- enlarged spleen
- jaundice
- muscle wasting
- excoriations (scratches or abrasions on the skin)
- ascites (fluid-filled belly)
- ankle swelling

### Extrahepatic Manifestations

Complications that do not involve the liver develop in 1 to 2 percent of people with hepatitis C; the most common is cryoglobulinemia, which is marked by

- skin rashes, such as purpura, vasculitis, or urticaria
- joint and muscle aches
- kidney disease
- neuropathy
- cryoglobulins, rheumatoid factor, and low-complement levels in serum

Other complications of chronic hepatitis C are

- glomerulonephritis
- porphyria cutanea tarda

Diseases that are less well documented to be related to hepatitis C are

- seronegative arthritis
- keratoconjunctivitis sicca (Sjögren's syndrome)
- non-Hodgkin's type, B-cell lymphomas
- fibromyalgia
- lichen planus

## Risk Factors and Transmission

HCV is spread primarily by contact with infected blood and blood products. Blood transfusions and the use of shared, unsterilized, or poorly sterilized needles, syringes and injection equipment or paraphernalia have been the main routes of the spread of HCV. However, some patients who acquire hepatitis C do not have a recognized risk factor or known exposure to infected blood or to drug use.

The most common risk factors for acquiring hepatitis C are

- injecting drugs, including having used injection drugs only once many years ago
- having a blood transfusion before 1992
- receiving clotting factor concentrates
- hemodialysis for kidney failure
- birth to an HCV-infected mother
- suffering a needle-stick accident from a person with hepatitis C

Other risk factors that have a slightly increased risk for hepatitis C are

- having sex with someone with hepatitis C or having multiple sex partners
- intranasal use of cocaine using shared equipment or paraphernalia

### Maternal-Infant Transmission

Maternal-infant transmission is not common. In most studies, less than 5 percent of infants born to HCV-infected mothers become infected. The disease in newborns is usually mild and free of symptoms. The risk of maternal-infant spread rises with the amount of virus in the mother's blood, if the mother also has human immunodeficiency virus (HIV) infection, or if there are complications of delivery such as early rupture of membranes and fetal monitoring. Breast-feeding has not been linked to the spread of HCV.

### Sexual Transmission

Sexual transmission of hepatitis C between monogamous partners appears to be uncommon. Surveys of spouses and monogamous sexual partners of patients with hepatitis C show that fewer than 5 percent are infected with HCV, and many of these have other risk factors for this infection. Spread of hepatitis C to a spouse or partner in stable, monogamous relationships occurs in less than 1 percent of partners per year. For these reasons, changes in sexual practices are not recommended for monogamous patients.

**WHEN TO SCREEN FOR HEPATITIS C?**

**Table 1. Persons for Whom HCV Testing Is Recommended**

- Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users
- Persons with conditions associated with a high prevalence of HCV infection, including:
    1. Persons with HIV infection
    2. Persons with hemophilia who received clotting factor concentrates before 1987
    3. Persons who were ever on hemodialysis
    4. Persons with unexplained abnormal aminotransferase levels
- Prior recipients of transfusions or organ transplants, including:
    1. Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
    2. Persons who received a transfusion of blood or blood products before July 1992
    3. Persons who received an organ transplant before July 1992
- Children born to HCV-infected mothers
- Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
- Current sexual partners of HCV-infected persons*

NOTE. Table adapted from Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention MMWR Recomm Rep 1998;47(RR-19):139.
*Although the prevalence of infection is low, a negative test in the partner
provides reassurance, making testing of sexual partners of benefit in clinical

# Serologic Tests

## Enzyme Immunoassay

Persons suspected to have hepatitis C should be tested for anti-HCV as an initial screening test. Anti-HCV is detected by enzyme immunoassay (EIA). The third-generation test (EIA-3) used today is more sensitive and specific than previous ones. As with all enzyme immunoassays, however, false-positive results are occasionally a problem with the EIA-3. Additional or confirmatory testing is often helpful.

The best approach to confirm the diagnosis of hepatitis C is to test for HCV RNA using a sensitive assay such as polymerase chain reaction (PCR) or transcription-mediated amplification (TMA). The presence of HCV RNA in serum indicates an active infection.

Testing for HCV RNA is also helpful in patients in whom EIA tests for anti-HCV are unreliable. For instance, immunocompromised patients may test negative for anti-HCV despite having HCV infection because they may not produce enough antibodies for detection with EIA. Likewise, patients with acute hepatitis may test negative for anti-HCV when first tested.

Currently available PCR assays will detect HCV RNA in serum down to a lower limit of 50 to 100 copies per milliliter (mL), which is equivalent to 25 to 50 international units (IU). **Genotyping of HCV**

There are six known genotypes and more than 50 subtypes of hepatitis C. The genotype is helpful in defining the epidemiology of hepatitis C. More important, knowing the genotype or serotype (genotype-specific antibodies) of HCV is helpful in making recommendations and counseling regarding therapy. Patients with genotypes 2 and 3 are two to three times more likely to respond to interferon-based therapy than patients with genotype 1. Furthermore, when using combination therapy, the recommended dose and duration of treatment depend on the genotype. For patients with genotypes 2 and 3, a 24-week course of combination treatment using peginterferon and 800 milligrams (mg) of ribavirin daily is adequate, whereas for patients with genotype 1, a 48-week course and full dose of ribavirin (1,000 to 1,200 mg daily) is recommended. For these reasons, testing for HCV genotype is clinically important. Once the genotype is identified, it need not be tested again; genotypes do not change during the course of infection.

## Quantification of HCV RNA in Serum

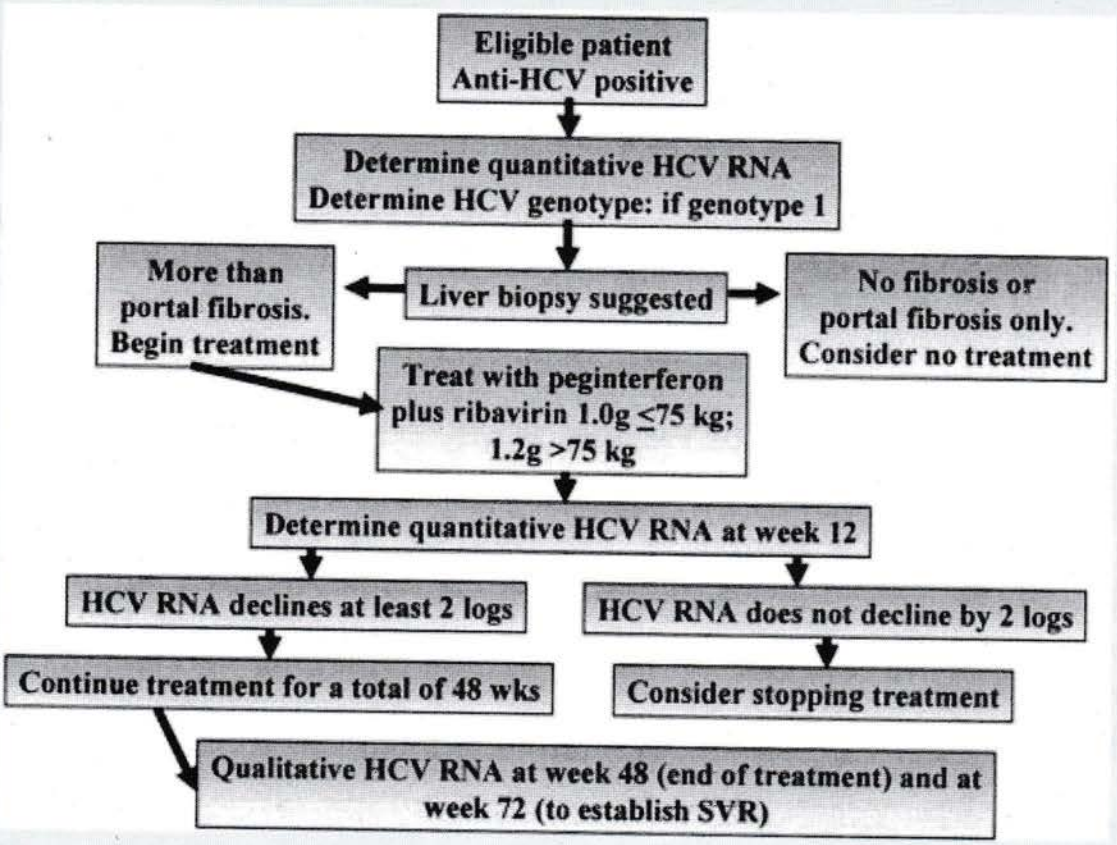
Several methods are available for measuring the concentration or level of virus in serum, which is an indirect assessment of viral load. These methods include a quantitative PCR and a branched DNA (bDNA) test. Unfortunately, these assays are not well standardized, and different methods from different laboratories can provide different results on the same specimen. In addition, serum levels of HCV RNA can vary spontaneously by 3- to 10-fold over time. Nevertheless, when performed carefully, quantitative assays provide important insights into the nature of hepatitis C. Most patients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 ($10^5$) and 10,000,000 ($10^7$) copies per mL. Expressed as IU, these averages are 50,000 to 5 million IU.

Viral levels as measured by HCV RNA do not correlate with the severity of the hepatitis or with a poor prognosis (as in HIV infection); but viral load does correlate with the likelihood of a response to antiviral therapy. Rates of response to a course of peginterferon and ribavirin are higher in patients with low levels of HCV RNA. There are several definitions of a "low level" of HCV RNA, but the usual definition is below 800,000 IU (~ 2 million copies) per mL.

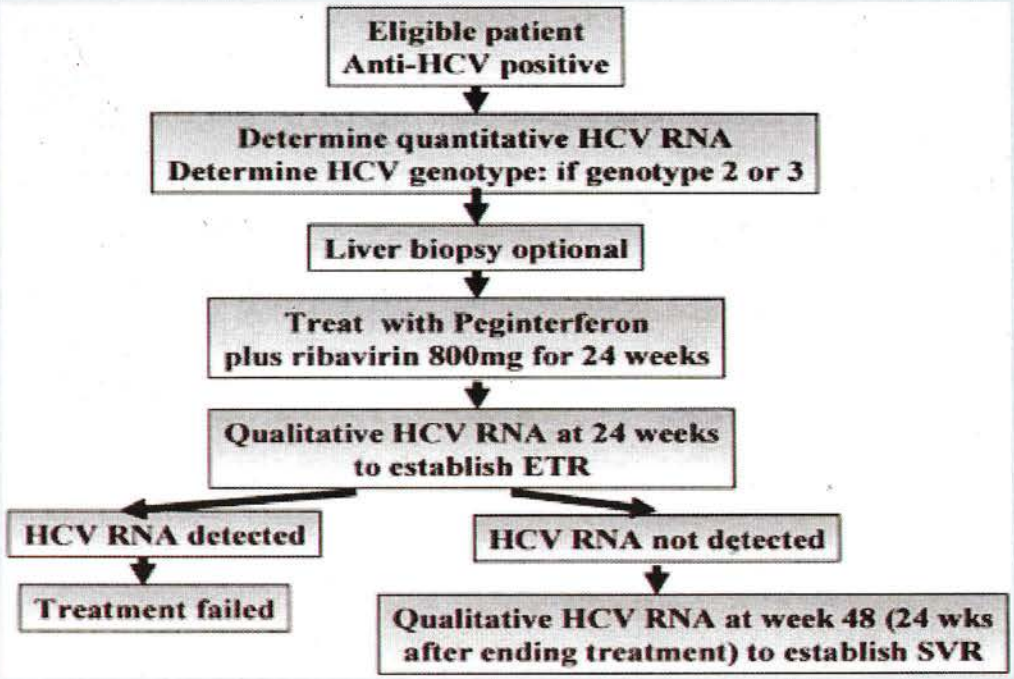
In addition, monitoring HCV RNA levels during the early phases of treatment may provide early information on the likelihood of a response. Yet because of the shortcomings of the current assays for HCV RNA level, these tests are not always reliable guides to therapy.

## Liver Biopsy

Liver biopsy is not necessary for diagnosis but is helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage. Hematoxylin and eosin stains and Masson's trichrome stain are used to grade the amount of necrosis and inflammation and to stage the degree of fibrosis. Specific immunohistochemical stains for HCV have not been developed for routine use. Liver biopsy is also helpful in ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.




**Sequential Steps in Hepatitis C: Genotype 1**




**Sequential Steps in Hepatitis C: Genotype 3 Treatment**

## Alpha Interferon

The therapy for chronic hepatitis C has evolved steadily since alpha interferon was first approved for use in this disease more than 10 years ago. At the present time, the optimal regimen appears to be a 24- or 48-week course of the combination of pegylated alpha interferon and ribavirin.

Alpha interferon is a host protein that is made in response to viral infections and has natural antiviral activity. Recombinant forms of alpha interferon have been produced, and several formulations (alfa-2a, alfa-2b, consensus interferon) are available as therapy for hepatitis C. These standard forms of interferon, however, are now being replaced by pegylated interferon (peginterferon).

## Ribavirin

Ribavirin is an oral antiviral agent that has activity against a broad range of viruses. By itself, ribavirin has little effect on HCV, but adding it to interferon increases the sustained response rate by two- to three-fold. For these reasons, combination therapy is now recommended for hepatitis C, and interferon monotherapy is applied only when there are specific reasons not to use ribavirin.

## Combination Therapy

Combination therapy leads to rapid improvements in serum ALT levels and disappearance of detectable HCV RNA in up to 70 percent of patients. However, long-term improvement in hepatitis C occurs only if HCV RNA disappears during therapy and stays undetectable once therapy is stopped. Among patients who become HCV RNA negative during treatment, some will relapse when therapy is stopped. The relapse rate is lower in patients treated with combination therapy compared with monotherapy. Thus, a 48-week course of combination therapy using peginterferon and ribavirin yields a sustained response rate of about 55 percent. A similar course of peginterferon monotherapy yields a sustained response rate of only 35 percent. A response is considered "sustained" if HCV RNA remains undetectable for 6 months or more after stopping therapy.

## Duration

The optimal duration of treatment varies depending on whether interferon monotherapy or combination therapy is used, as well as by HCV genotype. Patients with genotypes 2 and 3 have a high rate of response to combination treatment (70 to 80 percent), and a 24-week course of combination therapy yields results equivalent to those of a 48-week course. In contrast, patients with genotype 1 have a lower rate of response to combination therapy (40 to 45 percent), and a 48-week course yields a significantly better sustained response rate.

Patients who test HCV RNA negative within 4 weeks of starting therapy are considered "rapid responders." In several studies, rapid responders with genotypes 2 and 3 have been found to be able to stop therapy after 12 to 16 weeks (12 to 8 weeks early) and still achieve a high rate of response. Similarly, rapid responders with genotype 1 may be able to stop therapy at 24 weeks (24 weeks early) and achieve an excellent response rate. The consequence of early stopping, however, is a higher relapse rate and this approach of abbreviating therapy in rapid responders must be individualized based upon tolerance. **HCV-RNA<12-15IU**

## Who should be treated?

Patients with anti-HCV, HCV RNA, elevated serum aminotransferase levels, and evidence of chronic hepatitis on liver biopsy, and with no contraindications, should be offered therapy with the combination of peginterferon and ribavirin.

## Who should not be treated?

Therapy is inadvisable outside of controlled trials for patients who have

- clinically decompensated cirrhosisbecause of hepatitis C
- kidney, liver, heart, or other solid-organ transplant
- specific contraindications to either monotherapy or combination therapy

Contraindications to peginterferon therapy include severe depression or other neuropsychiatric syndromes, active substance or alcohol abuse, autoimmune disease (such as rheumatoid arthritis, lupus erythematosus, or psoriasis) that is not well controlled, bone marrow compromise, and inability to practice birth control. Contraindications to ribavirin and thus combination therapy include marked anemia, renal dysfunction, and coronary artery or cerebrovascular disease, and inability to practice birth control.

## Side Effects of Treatment

Common side effects of alpha interferon and peginterferon (occurring in more than 10 percent of patients) include

- fatigue
- muscle aches
- headaches
- nausea and vomiting
- skin irritation at the injection site
- low-grade fever
- weight loss
- irritability
- depression
- mild bone marrow suppression
- hair loss (reversible)

Most of these side effects are mild to moderate in severity and can be managed. They are worse during the first few weeks of treatment, especially with the first injection. Thereafter, side effects diminish. Acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) such as ibuprofen or naproxen may be helpful for the muscle aches and low-grade fever. Fatigue and depression are occasionally so troublesome that the dose of peginterferon should be decreased or therapy stopped early. Depression and personality changes can occur on peginterferon therapy and be quite subtle and not readily admitted by the patient. These side effects need careful monitoring. Patients with depression may benefit from antidepressant therapy using selective serotonin reuptake inhibitors. Generally, the psychiatric side effects resolve within 2 to 4 weeks of stopping combination therapy.