INTRODUCTION

The estimation of Hepatitis C virus (HCV) -infected individuals in Turkey is between 400,000 and 800,000 and approximately more than three-fourth of all infected individuals are unaware of their infection (1). HCV is primarily transmitted through percutaneous exposure to blood and blood products, mother-to-infant, contaminated devices shared with drug users and sexual transmission (2-5). HCV is not spread by hugging, holding hands, sneezing, coughing, or sharing eating materials or drinking glasses. HCV is not transmitted through water or food.

All individuals recommended for HCV testing should first be tested for HCV antibody (anti-HCV). A positive test result indicates active HCV infection (acute or chronic), past infection or a false-positive test result. HCV RNA testing is necessary to confirm active (current) infection.

I. GROUPS THAT NEED TO BE PRIORITIZED FOR CHRONIC HEPATITIS C VIRUS ASSESSMENT

I.A. High-Risk Behaviors

- Drug-injection and substance use
- Non-Intravenous (IV) drug addicts
- People with history of risky sexual behavior
  - Men who have unprotected sex with men
  - People with multiple partners
- Sex workers

I.B. High-Risk Exposures

- Long-term hemodialysis patients
- Occupational groups (healthcare, emergency medical, hairdressers, beauty salon workers, etc.)
- Children born to HCV-infected women
- People with percutaneous/parenteral exposures in an unregulated setting (tattoos and piercings, group circumcisions, manicure or pedicure performed under unhygienic conditions)
• People with a history of shared use of “personal hygienic items”,
• People with a history of dental procedures and medical interventions,
• People under risk of in-family contact,
• Prior recipients of transfusions or organ transplants,
  • People who have received blood or blood products, or underwent an organ transplantation before 1996,
• People living in shared closed environments (penitentiary facilities, childcare institutions, nursing homes, military barracks, etc.)

I.C. Other Instances
• Human Immunodeficiency Virus (HIV) infection
• Hepatitis B virus (HBV) infection
• Immunosuppressed individuals, who receive chemo/immunosuppressive therapy
• Unexplained chronic liver disease
• Solid organ donors

II. SPECIAL INTERVENTIONS FOR PRIORITY GROUPS
II.A. For Individuals in Risk Behavior Group:
• An anti-HCV test is recommended for HCV testing
• Performing anti-HCV test once a year
• Current HCV infection should be confirmed by a sensitive HCV RNA test if anti-HCV is positive

II.B. For Individuals in Risk Exposures Group:
• HCV testing is recommended
• Individuals with a negative anti-HCV and HCV RNA tests, who might have been exposed to HCV within the last 6 months, retesting for HCV RNA is recommended 6 months after the exposure
• In immunocompromised patients (hemodialysis patients, those using immunosuppressive agents, etc.), it is recommended to have HCV RNA tested once a year even anti-HCV is negative.
• Periodic testing should be offered to other individuals with ongoing risk factors for exposure to HCV

III. LABORATORY AND RADIOLOGICAL TOOLS TO BE USED IN DIAGNOSIS

III.A. General Laboratory Tests
Biochemical tests: Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin and total bilirubin levels.

Hematological tests: Complete blood count (CBC), international normalized ration (INR) level.

It is important to demonstrate liver damage by biochemical tests for diagnosis. Elevation of serum transaminases is generally in correlation with inflammation and fibrosis; however, normal serum aminotransferases levels do not rule out liver damage.

III. B. Serological Tests
Anti-HCV: Anti-HCV should be used as a screening test. Third or fourth generation “enzyme immunoassay (EIA) tests” need to be used. This test can be negative during the 3-4 weeks following the acquisition of the virus or in immunosuppressed individuals. Anti-HCV positivity continues after spontaneous or treatment-induced viral clearance. However, in some it might be disappeared.

Other serological tests: Anti hepatitis A virus (HAV) Immunoglobulin G (IgG), hepatitis B surface antigen (HBsAg), anti hepatitis B surface (HBs), anti hepatitis B core (HBc) IgG, Anti HIV

III.C. Virological Tests:
HCV-RNA (RT-PCR): Quantitative HCV-RNA can generally be detected within 1-2 weeks after acquiring the virus. HCV RNA testing is recommended prior to the initiation of antiviral therapy and during post-treatment follow-up (2-5). The cut-off level should be 15 IU/mL.

Viral genotype tests: HCV genotype and subtype should be identified to guide selection of the most appropriate antiviral therapy (5-7).

III. D. Radiological Tests
Abdominal ultrasound, computed tomography (CT) scan and magnetic resonance imaging (MRI) can assess liver surface nodularity, liver and spleen size and the presence of portal hypertension

III.E. Identification of Fibrosis Stage
• The severity of liver disease is a key factor in determining the initial and subsequent evaluation of patients with HCV infection. A liver biopsy can provide objective information regarding severity of hepatic necro-inflammation and fibrosis, and help exclude competing causes of liver injury. However, sampling error and observer variability limit its performance.
• Noninvasive methods include indirect and direct serum biomarkers (Fibrotest, APRI, FIB-4, etc.), transient elastography (MR elastography, fibroscan) used to estimate the degree of fibrosis. No single test is recognized to have high accuracy alone. The most efficient approach to degree of fibrosis assessment is to combine direct serum markers and transient liver elastography (8-9).
• A liver biopsy is not necessary to identify the stage of fibrosis in patients diagnosed clinical cirrhosis.

IV. DIAGNOSIS OF ACUTE HEPATITIS C
IV.A. Acute HCV infection may result from exposure to the virus through various routes as described above. Approximately, 20-50% of patients with acute HCV infection have spontaneous resolution of the infection (2-6). Anti-HCV antibody and HCV RNA testing are recommended when acute HCV infection is due to exposure (2-6).
i. A positive HCV RNA test in the setting of a negative anti-HCV test and/or a positive anti-HCV test after prior negative anti-HCV test are supported the diagnosis of acute HCV infection. Anti-HCV test may be negative during the first 3-4 weeks after exposure or in some immunocompromised patients due to impaired antibody production.

ii. HCV RNA testing may be transiently negative during acute HCV infection. If HCV RNA test is negative even a positive anti-HCV test, HCV RNA re-testing is recommended 12 weeks after initial testing. A low anti-HCV antibody titer may represent a false-positive result.

IV.B. A diagnosis of acute hepatitis C can be made when HCV RNA test is detectable in patients with a presentation of acute hepatitis (serum ALT level>10 times upper limit of normal and jaundice), who had previously a negative anti-HCV test (2-6).

The other causes of acute hepatitis should be excluded in patients suspected acute HCV infection.

V. DIAGNOSIS OF CHRONIC HEPATITIS C

The diagnosis of chronic hepatitis C (CHC) is defined as positive anti-HCV and HCV RNA testing for at least 6 months in patients with HCV infection (2-6). In some cases, there might be HCV RNA positivity by itself. Before the treatment, the severity of the disease is identified with invasive or non-invasive methods.

VI. TREATMENT INDICATIONS FOR CHC INFECTION

- The goal of antiviral treatment for HCV infection is to reduce liver-related morbidity and mortality by the achievement of virological cure. (2-6)
- Antiviral therapy is recommended for all CHC patients with positive anti HCV and HCV RNA testing, except those with a short life expectancy (less than one year). In Turkey, antiviral therapy is currently reimbursed for CHC patients with ≥F1 fibrosis (Ishak score).
- Decompensated patients should be managed by expert physician in liver transplantation (LT) unit. If MELD score is >20, LT should be planned and antiviral treatment should be postponed to the period after LT. However, if the transplantation waiting period is more than 6 months, antiviral treatment should be started before LT.

VII. TREATMENT DEFINITIONS

Sustained virological response (SVR): Sustained virological response (SVR) is defined as the continued absence of detectable serum HCV RNA levels at 12 and 24 weeks after completion of therapy. SVR is a marker for cure of HCV infection. Virological cure decreases in liver inflammation, reduces in rate of disease progression, improves portal hypertension and other clinical manifestations of advanced liver disease, reduces in the risk of hepatocellular carcinoma (HCC) and substantially improves quality of life. These reductions contribute to ultimately reductions in all-cause mortality. Therefore, CHC patients should be treated, preferably early in the course of disease before the development of severe liver disease and its complications.

Permanent virological response: SVR has been shown to persist in more than 99% of CHC patients followed more than 5 years

Relapse: Relapse is defined as undetectable serum HCV RNA at end of the antiviral treatment followed by a detectable HCV RNA after antiviral treatment discontinuation

VIII. PRE-TREATMENT EVALUATION

Pre-treatment evaluation should be made in all patients. CHC patients should receive education about interventions aimed his/her disease course and preventing HCV transmission. Patients should also be educated about the crucial importance of adherence to drugs, and the necessity for close supervision and laboratory tests during and after antiviral treatment. (2-6)

The following points should be covered in detail (2-6):
- Serum pregnancy testing is recommended for women of childbearing age prior to antiviral therapy that includes ribavirin.
- Vaccination against hepatitis A and B is recommended for all susceptible patients.
- Vaccination against pneumococcal infection is recommended to all cirrhotic patients.
- Screening for HCC is necessary in all cirrhotic patients.
- Staging of hepatic fibrosis is essential prior to antiviral therapy for facilitating an appropriate decision about HCV treatment strategy. Liver disease severity using the Child-Turcotte-Pugh (CTP) score should be assessed.
- The following laboratory tests are recommended within 12 weeks prior to initiate to antiviral therapy
  - CBC,
  - Serum ALT, AST, total and direct bilirubin, ALP and INR
  - Calculated glomerular filtration rate (GFR)
- Serum HCV RNA level, HCV genotype and subtype identification are recommended. The type, duration and response to treatment are affected by HCV genotype and subtype. Genotype 1 infection that cannot be subtype should be treated as genotype 1a infection.
- Assessment of potential drug-drug interactions with concomitant medications is recommended (http://www.hep-druginteractions.org.)
- All patients should be evaluated for HBV and HIV coinfections.
- Alcohol consumption and iv-drug use should be investigated and intervention to facilitate cessation of alcohol consumption and iv-drug use should be advised.
- Comorbidities including heart failure, renal failure, diabetes, autoimmune disease and extra-hepatic manifestations should be investigated.
- Testing for the presence of resistance-associated substitutions (RASs) should be performed in the initial antivi-
ral treatment and/or the retreatment. Basal NS5A resistance mutations should be tested in patients infected with genotype 1a prior to elbasvir treatment. Basal Q80K mutations should be tested in patients infected with genotype 1a prior to simeprevir treatment.

- Women of childbearing age should be counseled not to become pregnant while receiving a ribavirin-containing regimen, and for at least 6 months after discontinuation the treatment.
- All patients, who are not on antiviral therapy for HCV should be evaluated every 3-6 months interval for the status of their liver disease. The patients should also be checked for other conditions include diabetes, obesity and alcohol consumption that might deteriorated the liver functions.

IX. FOLLOW-UP DURING TREATMENT

IX.A. Routine Patient Follow-up

- Clinic visits are recommended during treatment to ensure adherence, and to monitor for adverse events and potential drug-drug interactions.
- On week 4
  - CBC
  - Hepatic injury and function tests
  - Creatinine level and calculated GFR
  - Quantitative HCV RNA testing

Asymptomatic increases in serum ALT level <10-fold should be closely monitored with repeat testing at 2-week intervals. If serum ALT levels persistently remain elevated, discontinuation of anti-viral therapy should be considered. A 10-fold increase in serum ALT level at any time during anti-viral therapy requires prompt discontinuation of therapy. Symptomatic (weakness, nausea, vomiting, jaundice) increases in serum ALT level <10-fold also requires prompt discontinuation of anti-viral therapy.

- At the end of treatment
  - CBC
  - Hepatic injury and function tests
  - Creatinine level and calculated GFR
  - Quantitative HCV RNA testing

- On 12 weeks after completion of anti-viral therapy
  - CBC
  - Hepatic injury and function tests
  - Quantitative HCV RNA testing

IX.B. Treatment Discontinuation Criteria

- If HCV RNA is positive at 4th week of the treatment, repeat HCV RNA testing is recommended at 6th week of the treatment. If HCV viral load has increased by >1 log_{10} IU/mL, discontinuation of treatment is recommended.

X. FOLLOW-UP AFTER TREATMENT IN PATIENTS HAVING SVR

- HCV viral load testing can be considered at 24 weeks or longer following the completion therapy.
- For non-cirrhotic patients, if HCV RNA is negative at 48 weeks after treatment, the follow-up can be discontinued.
- In patients with cirrhosis/severe fibrosis (metavir 3-4, Ishak ≥4) follow-up for HCC should be continued with ultrasonography and alpha-fetoprotein (AFP).
- In patients with an ongoing HCV transmission risk, HCV RNA should be tested once a year.
- HCV recurrence controls are not made in patients who are receiving chemo/immunosuppressive treatment or chemotherapy.

XI. FOLLOW-UP AFTER TREATMENT FOR PATIENTS WHO DO NOT HAVE SVR

- Should be evaluated for new treatments.
- HCC surveillance should be continued with abdominal ultrasonography and AFP every 6 months in patients with cirrhosis/severe fibrosis.
- Cirrhotic patients should be followed-up. Endoscopic examinations for portal hypertension are same in other cirrhotic patients.
- Non-cirrhotic patients are followed-up by CBC, biochemistry and INR test every 6 months.

The authors declare no conflicts of interest; no financial support was received for the conduct of this study.

ACKNOWLEDGMENTS

The authors thank Elif Sertesen and Şule Girmen for their kind assistance in English grammar edition.

REFERENCES

5. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. September 21, 2017 Available from: URL: http://www.hcvguidelines.org. [CrossRef]