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Hepatitis C Virus (HCV) Infection: Screening, Diagnosis, Therapy and Prevention

Khanduri Naresh* and Negi Sonali

School of Allied Sciences, Dev Bhoomi Uttarakhand University, Dehradun, Chakrata Road, Manduwala, Naugaon, 248007, Uttarakhand, India
Email ID: sonalinegi03091996@gmail.com, sops.naresh@dbuu.ac.in
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ABSTRACT

Infection with the HCV has become a big health issue worldwide. Methods based on virological and genetic aspects play an critical part in diagnosis & treatment evaluation. The traditional algorithm for diagnosing viral hepatitis consists of a test based on serum followed by a test based on genetic material. This test sequence is time consuming and not sustainable in low resource environments. In case of managing chronic HCV infection, significant updation in diagnostic methods as well as antiviral therapy plays an important role. By understanding the life cycle of hepatitis C virus, it is feasible to create antiviral that operate directly on the virus. In addition, some newer treatments are available that are subjected to a combination of antivirals and/or interferon-free regimens. But continuous advancement in diagnostics led to the replacement of regimen based on interferon with interferon-free regimen. In this review, we have summed up the outline of HCV infection, its transmission ways, screening methods. In addition, an outline on treatment and prevention measures is also provided

Keywords: Hepatitis C, screening assays, prevention, treatment

*Corresponding Author:

Dr. Naresh Khanduri
Assistant Professor, Dev Bhoomi Medical College of Paramedical Sciences,
Dev Bhoomi Uttarakhand University, Dehradun, Chakrata Road,
Manduwala, Naugaon, 248007, Uttarakhand, India
Email ID: sops.naresh@dbuu.ac.in

1. INTRODUCTION

HCV, (Hepatitis C virus) is an RNA virus in the Flaviviridiae family. It is a hepatotropic virus, major responsible agent of liver disease with serious morbidity & mortality worldwide. All over the world, chronic HCV infection affects 71 million people and more than 400,000 people become infected each year**.** [1] In countries with low to middle income, the load of hepatitis C virus infection is very high. It is reckon that there are approximately 6 million people abide with hepatitis C virus in India alone, many of which are ignorant of their condition**.** [2] Acute hepatitis is the initial infection caused by HCV, but slowly develops in chronic hepatitis in over 80% of those having the infection of HCV. [3-4] In 2016-2021, WHO approved the Global Health Strategy (GHSS) on viral hepatitis, which focuses on elimination of viral hepatitis by 2030. The goal is to cut the rate of new cases and related deaths by 90% & 65%, separately. [5] Best use of drugs against the viral infections can help around 95% of people with HCV, thus decreases mortality related with cirrhosis & liver cancer. Although, little access to early & precise testing, diagnosis & treatment is the difficult obstacle in reaching the aim. [6] the US Centres for Disease Control and Prevention (CDC) suggested examination of entire patients who are more prone for infection related to HCV by anti-HCV assay or, in special cases with the help of RT-PCR. [7]

Early diagnosis & therapy of infection related to HCV can minimize the possibility of disease of liver, mortality & check the spread of current infections.[8-9]. The initial stride in growing approach to HCV cure is for persons who are having HCV infection of chronic stage. The current infection of HCV can be determined by testing based on presence of antibodies, which can be then confirmed using molecular based methods or by assay that can help in detecting core antigen of HCV. [1] It seems out that the basis of detecting HCV are molecular & serological tests. Molecular assays for nucleic acid enhancement (NAT) based on RT-PCR for HCV detection in RNA in different specimens which includes mainly blood and as well as other body fluids. [10] However, NAT-based testing is uneconomical and is generally not suitable for large-scale HCV screening for rapid diagnosis. [11] Conversely, serological tests are often designed to detect HCV Serum or plasma antibodies: Antibodies are rapidly removed from venipuncture therefore, for mass screening in general population, serum based tests are best. Currently, several enzyme-based serological tests (EIA) are commonly used to detect HCV in clinical specimens. [12] In numerous tests, longer result times, high cost, tool size, and the need for very skilled technicians restricting the use of current assay in limited assets areas. [13-14]. This review purpose is to provide an outline HCV infection, main ways of its transmission, assays for screening, treatment & preventive measures.

1.1. Geographical Distribution

HCV has been reported from all around the world. The WHO Eastern Mediterranean Region and the WHO European Region are the most troublesome areas, with an estimated prevalence of 2.3% and 1.5% in 2015, respectively. Hepatitis C virus infection rates in another WHO zone range from 0.5% - 1.0%. Based on the country, HCV infection may be confined in a specific population. [1] There are several genotypes of HCV virus & their dissemination varies by parts. But, in many countries the distribution of genotypes is still unknown. [1] Six genotypes of HCV have been identified, with genotype 1 accounting for 46% of all cases worldwide, genotype 3 for 22%, and genotypes 2 and 4 for 13%. According to the HCV genotype categorization in India, genotype 3 is the most prevalent (61.8%) and genotype 1 is the second-most prevalent (31.2%). In 0.05–4.5% of instances, the genotypes 2, 4, 5, and 6 were identified. [15] According to reports, the frequency of the HCV in India's general population ranges in 0.22 and 1.8%. [15]

1.2. Structure of Hepatitis C Virus

HCV is a positive stranded, enveloped virus with the genetic material i.e RNA located within nucleocapsid which consists of a core protein and lipid bilayer. [16] The RNA genome size is between 9.6-12.3 thousand nucleotides. In addition, it has an ORF which codes a multiple protein consist of more than 3000 amino acids. ORF in the 5' is flanked by untranslated region (UTR) of 95 nucleotides in length while on the 3', the length is 555 nucleotides. [17] Further, 5' untranslated region also have an IRES (internal ribosomal entry site). [18] With respect to the genotypes, the open reading frame of hepatitis C virus has 9024-9111 nucleotides and also encodes 3 structural proteins. Moreover, some non-structural proteins like NS2, NS3, NS4A, NS4B, NS5A and NS5B are in charge of the reproduction of viruses as well as their life cycle. Furthermore, p7, a different protein, appears to have non-structural action as well. [19]

1.3. The Hepatitis C virus's life cycle

The cycle of HCV start with the attachment or adhesion to the host, then entry to the liver cells and then step of fusion. Next step is the translation & replication, then assembly of virus and finally release. [20] Circulating HCV particles travel to the pores in the liver sinusoidal endothelium and communicate with hepatocytes. Upon contact, viral particles then interacts on the surface of hepatocytes via attachment factors. [21] This binding to hepatocytes was at first assume to engage the heparin sulfate proteoglycan expressed on the surface of hepatocytes. [22] HCV particle connects with a number of cell-

specific receptors and an entrance element in a multistep process after adhering to the cell surface. [21] It is ingested by clathrin-mediated endocytosis after adhering to various parts of the host cell, and fusion takes place in the primary endosome. [23] RNA replication and translation occur once HCV has entered the body. A highly ordered replication complex with various non structural parts where fresh viral RNA is formed. It also plays a part in virus particles collection released from the host cell. [21] Both the above phases signal the ending of the viral cycle.

1.4. Symptoms of HCV infection

HCV infection mainly affects liver and causes its inflammation. In acute HCV infection, appearance of clinical signs or symptoms occurs for six months or less after primary contact with the virus. [24] Therefore, the diagnosis of infection in this phase is difficult. [25] When HCV infection does not go away within six months, it become chronic and therefore subsequently; result in cirrhosis and hepatocellular carcinoma.[15] HCV period of incubation is ranges from 2 weeks-6 months. About 80% of people have no symptoms after the initial infection. Symptoms include fever, lethargy, nausea, vomiting, abdominal discomfort, joint pain, dark urine, jaundice and grey stools. [26]

1.5. Modes of Transmission

Contact with an infected person's blood or body, use of drugs via injection, implementation in nursing of patient or medical laboratory work, identify a sexual partner or family member having previous infection with HCV are the main transmission pathways. [27] However, compared to the other underlying causes, the chance of STIs and mother-to-child transmission of HCV is lower during pregnancy. HCV RNA in serum can be used to assess infection stage as well as the likelihood of a chronic infection or transmissible infection. [28-29]

2. Screening of HCV infection

Screening for HCV infection entails detecting and confirming HCV in an infected person's serum/plasma using several serology-based and molecular techniques. [30-31]

2.1. Serological antibody assays

The initial step in detecting HCV is to check the serum for HCV antibodies. Antibody test findings are classified as reactive (positive) or non-reactive (negative). [32] In past few years, different generations of hepatitis C virus antibody tests have been developed with every generation enhancing the sensitivity and specificity of the HCV antibody assay. [33]

2.1.1. First-generation assay: The basis of these assays is the anti-HCV antibodies binding to the NS4 epitope region (C100-3). These methods can detect about 80% of HCV IgG in postpartum cases. Consequently, its sensitivity and specificity were very low. Among the low-risk population, its false-positive rate was reported at 60%. [34]

2.1.2. Second-generation assays: Recombinant (structural) basic proteins, NS3 and NS4 have been used as anti-HCV binding proteins. Second-generation methods reduced the HCV window period to 10 to 24 weeks. [35]

2.1.3. Third-generation assays: Immunosorbent comprises regenerating proteins from core regions: NS3, NS4, and NS5. More than 99% of the specificity was reported in this test category**.** In India, the usage of third generation serological test is required for the detection of hepatitis c virus infection in blood donation units prior to transfusion under the 1940 and 1945 Medicines and Cosmetics Acts. [36]

2.1.4. Fourth-generation assays this includes antigen-antibody assays that detect anti-HCV antibodies as well as HCV antibodies simultaneously. These tests are quite sensitive and account for the reduction in window period. These tests have an average window period of 26.8 days. [35]

The second generation anti-HCV enzyme immunoassay (EIA-2) is the most extensively utilised screening test for HCV infection among the three generations of EIAs. [37]. Enzyme immunoassays and rapid diagnostic assays right now are the most popular common serological tests utilized to detect HCV antibodies in blood donors or to identify hepatitis C virus antigens. [38] The CDC proposed that every single positive antibody examination has to be confirmed by an HCV RNA test. [39-40]

2.2. HCV Nucleic Acid Testing

Antibody testing assays lack the highest level of specificity and sensitivity to distinguish between active & settled infections. As a result, molecular approaches are crucial in the management of hepatitis virus C infection for precise diagnosis. [39] They are advised to have HCV RNA confirmed in patients tested positive for HIV. This test is also utilized to validate the presence of HCV in the blood in seropositive but immunocompromised patients, as antibodies in infants can even produce false positive findings till that infant attained age of 18 months and to find out the reference value prior to antiviral therapy. Qualitative and quantitative molecular methods (viral load) for acute and chronic infection testing have been developed. [41] It is based on Polymerase Chain Reaction technology that helps reduce the time between HCV infection and detection of antibody. [38]

3. Treatment options

Treatments for hepatitis C are developing and available treatments are based on combination of different agents or immunotherapy. Majority of current medications is combination therapy which is any type interferon-based or non-interferon-based. Nevertheless, HCV genotype and viral load prior to treatment are two crucial factors of response to antiviral therapy. [42]. Ledispasvir-sofosbuvir and sofobuvir-velpatasvir are two extensively used interferon-free treatment medicines for HCV genotype 1, for treating-new or old suffering individuals because of high SVR rates achieved. [43] Treating with a fixed dose of instapasvir-sofosbuvir in new patients for 12 weeks, resulted in SVR rates above 95%. [44] Unlike ledispasvir-sofosbuvir, a 12-week treatment with sofobuvir-velpatasvir results in high SVR values among a large number of people infected with sofobuvir-velpatasvir and daclatasvir-sofosbuvir is indicated for patients with compensated cirrhosis. [45] In contrast to ledispasvir-sofosbuvir, a 12-week course of sofobuvir-velpatasvir resulted in high SVR rates among many individuals infected with sofobuvir-velpatasvir. In patients with symptom less cirrhosis, the use of daclatasvir-sofosbuvir regimen is recommended. Despite the significant incidence of HCV genotype 3 in the world, it is regarded the most treatment-resistant genotype. [46] To achieve a substantial SVR rates in such type of cases, pegylated interferon (PEG-IFN) alpha with ribavirin is the only available regimen. [47] Daclatasvir plus sofosbuvir, on the other hand, has recently been proposed as a treatment for HCV patients with hepatitis C virus genotype 3. [48]

4. Strategies to control HCV

Updating testing of HCV & operation: this could be achieved by preparing standard protocols to escort HCV testing & forwarding to care; **Strengthen public HCV control programs**: Appropriately collection of data at the level of community to help local programmers to precisely handle health issues related to HCV; **Testing for high risk groups**: Covering of groups connected to a very high possibility of getting an hepatitis C virus infection (eg, patients with haemodialysis and intravenous Drug Use); **Progress of HCV vaccines**. Because of high levels of heterogeneity and mutation in the HCV genome, developing an effective vaccine remains in uncertain. The most recent vaccine options, includes recombinant protein and peptide vector-based vaccines, has promised to enter the second half of clinical trials; **Dual approach**: Twofold perspective of reducing the incidence of naive cases and treating old cases is expected to play a significant part in reducing burden of disease. [49-51]

5. Preventive measures

As there`s no vaccine that can provide protection against this virus, but with the right preventive measures, we can prevent an infection in our self & others. [52] Sometimes, razors, scissors, or nail clippers can cause minor cuts. According to some previous researchers; people who inject drugs are more prone to new HCV infections. HCV infection not only spread by sharing needles or by getting a tattoo, it can also spread via unexpected contact with an infected individual blood. So one need to be very careful working as healthcare professional, HCV is hardly transmitted via vaginal contact, but measures are taken to protect others using condoms. HCV can be spread via menstrual flow, so avoid sex at this time of month, says NHS. It is also recommended to wear to condom during anal sex too as anal sex can result in small tears around the rectum. This can cause minor bleeding & spread the virus from person to person. [53, 54]

CONCLUSION

Hepatitis C is a major health problem worldwide, but it is now possible to eradicate it through direct antiviral treatment. Achieving eradication will need increased diagnosis and relevance to care as well as universal avenue to available diagnostics. HCV diagnosis should be as reliable as possible, as a positive result has a profound effect on the life of the affected person. Different diagnostic tests included serological tests, which include antibodies to HCV such as ELISA and RIBA and Nucleic Acid Tests (ATS), which include analysis of viral RNA load. Molecular methods are used to diagnosis, observance of active hepatitis C virus replication because the virus cannot be cultured. In brief, effort to develop more effective treatments, despite recent progress, it must remain a top priority. The best solution for an HCV epidemic worldwide is to develop an effective vaccine. Hepatitis C infection testing and diagnosis is the doorway to prevention and therapeutic applicability. It is necessary to identify the main populations infected with HCV so that chain of infection can be broken. Further, increasing the scale of blood safety programs and reducing health-related transmission continue to be key prophylactic steps in eradication programs.

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