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(REVIEW ARTICLE)

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Unveiling Hepatitis C: Causes, Impact and advances in treatment

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Abstract

Hepatitis C Virus (HCV) infection continues to pose a major global health issue, with around 58 million chronic cases reported worldwide and about 1.5 million new infections each year. This virus is a primary contributor to chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC), leading to approximately 290,000 deaths annually (WHO, 2022). The introduction of direct-acting antiviral (DAA) therapies has transformed HCV treatment, with sustained virologic response (SVR) rates surpassing 95% across various genotypes. However, challenges remain in meeting the World Health Organization's target of eliminating HCV as a public health threat by 2030. Key obstacles include low diagnosis rates, as only 21% of those infected with HCV are aware of their condition, and restricted access to treatment, especially in low- and middle-income countries (LMICs).

This article reviews the latest epidemiological trends related to HCV, focusing on the disparities in disease burden and access to healthcare. It discusses innovative diagnostic methods, such as point-of-care testing, and emphasizes the importance of universal screening programs in areas with high prevalence. Additionally, we look at new therapeutic strategies, including pan-genotypic DAAs and their effects on marginalized communities. Lastly, we examine public health initiatives aimed at enhancing HCV prevention, such as harm reduction programs and vaccination efforts for co-infections like hepatitis B.

By integrating findings from recent studies and reports, this article highlights the necessity for collaborative global efforts to address the challenges of HCV elimination. Strategies that emphasize prevention, early detection, and fair access to treatment are crucial for alleviating the HCV disease burden and reaching elimination goals.

Keywords: hepatitis C; Viral infection; Hepatocellular carcinoma; Vascular disorders; Liver biopsy

1. Introduction

Hepatitis C is mainly affecting liver and it is blood-borne viral infection the hepatitis C virus (HCV), primarily transmitted through blood-to-blood contact. The infection can be acute to chronic, with a significant proportion of individuals responsible for chronic liver disorders and complications are cirrhosis and liver cancer (hepatocellular carcinoma).HCV is a single-stranded RNA virus that belongs to the Flaviviridae family. Infected individuals may remain asymptomatic for years, with some progressing to chronic infection, liver fibrosis, cirrhosis, or liver cancer.

1.1. Etiology

Main cause of HCV is injecting of infected blood, sexual intercourse and it can be placental transmission during childbirth. Hepatitis C virus (HCV) enters hepatocytes via receptors such as CD81, SR-B1, and CLDN1. mostly involved developing countries which have more middle class and lower middle-class families and those countries who is not able

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to afford expensive treatment and reuse drug injections equipment. And in this country's healthcare departments aren't able to prevent or provide right suggestions and prevention programs to each and every side and continuously they are using unsafe healthcare care exposures. And when a Travelers visits, they have high risk of contract and transmission of such diseases like HCV and blood to blood contact disease.

1.2. Transmission

HCV is mainly spread through contact with infected blood. The primary transmission routes include:

- Injection Drug Use: The sharing of contaminated needles is the most prevalent method of transmission in many regions.
- Healthcare-Related Transmission: Unsafe medical practices, such as reusing syringes or failing to properly sterilize medical equipment, have historically played a significant role in the spread of HCV.
- Blood Transfusions and Organ Transplants: Prior to the introduction of HCV screening in the 1990s, cases related to transfusions were quite common.
- Maternal-Fetal Transmission: Vertical transmission from mother to child occurs in about 5-6% of cases, with increased rates in mothers who are co-infected with other viruses, such as HIV.
- Sexual Transmission: While less frequent, it can happen, especially among men who have sex with men (MSM) or individuals with other sexually transmitted infections.

1.3. Pathophysiology

Hepatitis C virus (HCV) infection triggers a complex interaction between viral replication and the host's immune responses, leading to liver inflammation and, eventually, significant liver damage over time.

1.3.1. Viral Entry and Replication

HCV mainly targets hepatocytes in the liver. The virus binds to specific receptors on the surface of host cells, such as CD81, scavenger receptor class B type I (SR-BI), claudin-1, and occluding, which helps it enter the cell. Once inside, HCV releases its positive-sense single-stranded RNA genome, which is then translated into a polyprotein. This polyprotein is cleaved by viral proteases, including NS2-3 protease, into structural and non-structural proteins that are crucial for viral replication. The replication process involves creating a replication complex associated with rearranged cytoplasmic membranes, particularly the endoplasmic reticulum, resulting in the production of new viral particles.

1.3.2. Immune Response and Chronic Infection

The immune response of the host to HCV often fails to eliminate the virus, leading to chronic infection. The virus uses several strategies to evade the immune system, such as high mutation rates that produce diverse viral quasi-species and the presence of hyper-variable regions in envelope glycoproteins, which make it difficult for antibodies to neutralize the virus effectively. Furthermore, HCV can alter host immune responses, which aids in its persistence.

1.3.3. Liver Inflammation and Fibrosis

Chronic HCV infection causes ongoing liver inflammation, mainly due to immune-mediated processes. This inflammatory environment activates hepatic stellate cells, resulting in fibrogenesis and the development of liver fibrosis. Over time, continued fibrogenesis can lead to cirrhosis, marked by extensive scarring of liver tissue and compromised liver function.

1.3.4. Progression to Hepatocellular Carcinoma (HCC)

People with cirrhosis caused by HCV face a higher risk of developing hepatocellular carcinoma (HCC). While the precise ways in which HCV leads to liver cancer are not completely clear, factors such as chronic inflammation, continuous liver cell regeneration, and the direct impact of viral proteins are believed to contribute.

1.3.5. Conclusion

The pathophysiology of HCV involves a complex interplay between the strategies of viral replication and the responses of the host's immune system, resulting in chronic liver disease, fibrosis, and an increased risk of liver cancer. Gaining insight into these mechanisms is essential for creating effective treatment strategies and interventions.

1.4. Signs and symptoms

Hepatitis C Virus (HCV) infection can show a variety of clinical features, ranging from cases that show no symptoms to those with significant liver damage, such as cirrhosis and hepatocellular carcinoma (HCC). The disease's progression can be divided into acute and chronic phases, with symptoms varying based on the level of liver damage and any extrahepatic manifestations.

Acute HCV infection occurs within the first 6 months after exposure to the virus, but it is frequently underdiagnosed because most individuals do not show symptoms.

1.4.1. Symptoms in Acute Phase

Around 20-30% of people with acute HCV infection may experience symptoms, which can include

- Fatigue
- Fever
- Nausea and vomiting
- Loss of appetite
- Abdominal pain, especially in the upper right quadrant
- Dark urine
- Pale or clay-colored stools
- Jaundice (yellowing of the skin and eyes)
- Myalgia or arthralgia (muscle and joint pain)

1.4.2. Clinical Course

Approximately 15-25% of acute cases resolve on their own without developing into chronic infection. Many cases go unnoticed due to mild symptoms or a complete absence of symptoms.

Chronic infection occurs in 75-85% of cases that do not spontaneously clear the virus. This chronic HCV infection can last for decades and may result in significant liver damage over time.

1.4.3. Early-Stage Chronic HCV

In its early stages, chronic HCV often shows no symptoms or presents with vague symptoms, such as:

- Persistent fatigue
- Mild abdominal discomfort
- Depression or mood disturbances

1.4.4. Signs and Symptoms of Advanced Liver Disease

As the infection advances, signs of liver dysfunction become noticeable, particularly in cases of cirrhosis or liver failure. These signs include:

- Ascites (fluid buildup in the abdominal cavity)
- Edema (swelling in the lower limbs)
- Spider angiomas (spider-like blood vessels on the skin)
- Jaundice
- Pruritus (intense itching)
- Easy bruising or bleeding due to impaired clotting factor production
- Hepatic encephalopathy (confusion, disorientation, or altered mental state due to toxin accumulation)

1.4.5. Progression to Hepatocellular Carcinoma (HCC)

Chronic HCV is a major cause of HCC, particularly in individuals with long-term cirrhosis. Symptoms may include unexplained weight loss, increasing abdominal pain, or jaundice.

1.4.6. Extrahepatic Manifestations of HCV

HCV is a systemic disease that can lead to complications outside the liver. These extrahepatic manifestations can affect up to 40% of individuals with chronic HCV and include

1.4.7. Vascular and Immune-Mediated Disorders

Cryoglobulinemia: This condition can cause vasculitis, resulting in symptoms like fatigue, rashes, and joint pain.

- Systemic vasculitis.
- Renal Manifestations
- Membranoproliferative glomerulonephritis, which is marked by proteinuria and hematuria.
- Endocrine Disorders
- Insulin resistance and type 2 diabetes mellitus.
- Dermatological Conditions:
- Lichen planus (characterized by an itchy rash).
- Porphyria cutanea tarda (which leads to skin sensitivity to sunlight and blistering).
- Neurological and Psychiatric Disorders:
- Peripheral neuropathy.
- Depression and cognitive impairment

1.5. Diagnosis and testing

There are mainly Two types of diagnosis tests we do: IgG assays test it is for detection of HCV antibodies, and second we can do nucleic acid amplification to determine HCV RNA in blood of infected patients

1.5.1. Serological test includes

- Anti-HCV Antibody (Anti-HCV): screening test in initial stage to detect antibodies against the HCV.
- Anti-HCV by ELISA
- Molecular test;
- HCV RNA by PCR (Polymerase Chain Reaction)
- HCV Genotype Testing

1.5.2. Liver biopsy test

Treatment and prevention are necessary for hepatitis C includes, treatment is necessary to cure the symptoms for spreading and preventing liver damage. medications, including antiviral sofosbuvir and daclatasvir, are given. In some cases, patients' immune system fights with the infection on their own and they do not need treatment. Protease Inhibitors (e.g., glecaprevir, grazoprevir): Inhibit the NS3/4A protease.

1.5.3. preventing viral replication.

NS5A Inhibitors (e.g., ledipasvir, daclatasvir, velpatasvir): Inhibit the NS5A protein that is responsible for viral RNA replication and assembly.

NS5B Inhibitors (e.g., sofosbuvir, dasabuvir): Inhibit the RNA polymerase enzyme, preventing viral replication.

Treatment of chronic HCV with pegylated interferon (PegIFN)-alpha and ribavirin (RBV) containing regimens is absolutely contraindicated in: Uncontrolled depression, psychosis or epilepsy; pregnancy; severe concurrent medical diseases including retinopathy, autoimmune thyroid disorders; liver cell failure.Treatment durations typically range from 7 to 14 weeks, depending on the individual's liver health.

Some of the methods for prevent hepatitis C include

- Use of healthcare injections in safe way
- disposal of needles and medical waste after use
- safety for nurses and staff who inject needle.
- donated blood testing before taking
- Training of healthcare services
- safe sex by using barrier methods.

* HCV Prevention Guidelines and 2030 Goals;

The 2030 goal for Hepatitis C elimination is ambitious but achievable. With global screening efforts, universal access to DAAs, safety and guidance programs for healthcare providers who inject drugs, and public health policies that ensure affordable treatment, it can play a major role in prognosis;

- Prevention through harm reduction, safe blood practices, and vaccination.
- Early diagnosis and rapid access to treatment.
- Affordable and scalable access to DAAs in low- and middle-income countries.

By 2030, the goal is to reduce new HCV infections, increase diagnosis and treatment rates, and significantly reduce hepatitis-related morbidity and mortality globally.

- Breastfeeding is safe in HCV positive mother. Sexual transmission is not seen in manager nous relation. but in polygamous, situation, transmission may occur.
- -There are 6 Genotypes present in Hepatitis C virus and Genotype 1 is most common type of Genotype in USA.
- Hepatitic c is most common cause of chronic hepatitis. While Hepatitis E is most common cause of Acute viral hepatitis.
- In case of Hepatitis c 85% case becomes Chronic. Out of 85% cases, 25% leads to Cirrhosis and End stage liver disease and risk of hepatocellular Carcinoma increases.
- Even with normal to modest elevations of Aminotransferase in HCV increases risk of Progression of Cirrhosis so Antiviral therapy is necessary here because if cirrhosis becomes decompensated then mortality rate increases.

2. Geographical distribution

Hepatitis C virus infection occurs in all WHO regions. The highest burden of disease is in the Eastern Mediterranean Region with 12 million people chronically infected. In the South-East Asia Region (9 million), European Region (9 million) and the Western Pacific Region (7 million) people are chronically infected. Eight million people are chronically infected in the African Region and 5 million the Region of the Americas.

Time Period	Regions Affected	Key Data Points	Sources
1990s - Early Data	- **High Prevalence**: Sub-Saharan Africa, Central & East Asia, Eastern Europe. - **Low Prevalence**: North America, Western Europe, Oceania.	- Global prevalence ~3%, concentrated in high-risk groups (e.g., intravenous drug users, blood transfusions). - Lack of screening in developing countries.	WHO (1990), CDC (1995).
2000s - Expanded Data	- **High Prevalence**: Egypt, Southeast Asia, Russia. - **Moderate Prevalence**: Latin America, Mediterranean. - **Low Prevalence**: North America, Western Europe.	- Estimated 170 million people globally infected by 2000. - Improved blood safety measures reduce transmission in developed countries.	WHO Hepatitis C Fact Sheet (2002), Global Hepatitis Report (2017).
2010s - Awareness & Programs	- **High Prevalence**: Egypt, Central Asia, South Asia, Eastern Europe. - **Moderate Prevalence**: Latin America, Sub-Saharan Africa, Southeast Asia. - **Low Prevalence**: Western Europe, North America.	- Global prevalence ~1.5%. - Introduction of Direct-Acting Antivirals (DAAs) improves treatment rates. - WHO's elimination strategy launched (2016).	WHO Global Hepatitis Report (2016), WHO Global Health Sector Strategy (2016-2021).
2020s - Elimination & New Treatments	- **High Prevalence**: Egypt, Central Asia, parts of Eastern Europe. - **Low to Moderate Prevalence**: Western Europe, North America, Australia.	- WHO targets global hepatitis C elimination by 2030. - Affordable DAAs increase global treatment access. - Focus on harm reduction in high-prevalence areas.	WHO Global Hepatitis Report (2022), CDC (2023), WHO Hepatitis Strategy (2023).

Figure 1 This image has detailed view of geographical distribution of Hepatitis C in different time periods

Category	Baseline (2017)	2025 Goal	2030 Goal
Acute HCV Infections	44,700	≤35,000 (↓22%)	≤4,400 (↓90%)
HCV-related Death (rate*)	4.13	≤3.00 (↓27%)	≤1.44 (↓65%)
New HCV in PWID (rate*)	2.3	≤1.7 (↓26%)	≤0.2 (↓90%)
HCV Clearance (%)	43% (2013-2016)	≥58% (↑35%) (2021-2024)	≥80% (↑86%) (2025-2028)

*Rates are per 100,000 population
2025 goals are based on 2023 data, and 2030 goals are based on 2028 data

Figure 2 Goals for the treatment for upcoming years

3. Results and discussions

* Histological findings: In chronic hepatitis C, inflammation is typically found in the portal areas of the liver, which can extend into the periportal regions. Infection spread after the immune response to the virus .inflammation at the interface between the portal tracts and the surrounding liver parenchyma.Hepatocellular ballooning, necrosis, and apoptosis (cell death) may be observed, contributing to the damage to liver tissue.

*Laboratory findings: Elevated ALT and AST (usually more than 2-3 times the normal range)

AST/ALT ratio is typically <1 in chronic Hepatitis C. Positive test confirms active infection and helps measure viral load. Anti-HCV Antibodies: Positive indicates exposure to HCV but not necessarily active infection. Confirm with HCV RNA testing. Elevated bilirubin: May indicate liver dysfunction. Low albumin: Seen in advanced liver disease.Prolonged prothrombin time (PT)/INR: In cirrhosis or advanced liver disease. Low platelet count: Suggestive of portal hypertension or advanced cirrhosis. APRI (AST to platelet ratio index) and FIB-4: Non-invasive markers to assess fibrosis stage.

* Imaging findings: Ultrasound: Hepatomegaly (enlarged liver) in early stages. Cirrhosis in advanced stages, with irregular liver contours and shrunken liver. Splenomegaly (enlarged spleen) due to portal hypertension. Ascites (fluid accumulation in the abdomen) in decompensated cirrhosis.Hepatocellular carcinoma (HCC) may appear as hypoechoic masses in cirrhotic livers.

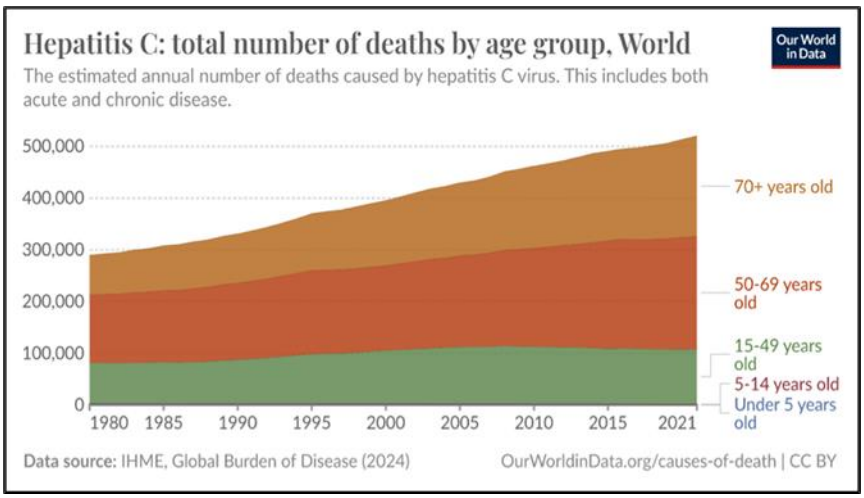

Figure 3 Total number of deaths in world according to age group based on 2024 survey

Elastography (FibroScan): Increased liver stiffness (measured in kPa) correlates with fibrosis or cirrhosis.

CT/MRI (less commonly used for diagnosis); CT/MRI may show liver atrophy, portal hypertension, splenomegaly, and ascites in advanced disease. HCC can be identified as a mass with contrast enhancement.

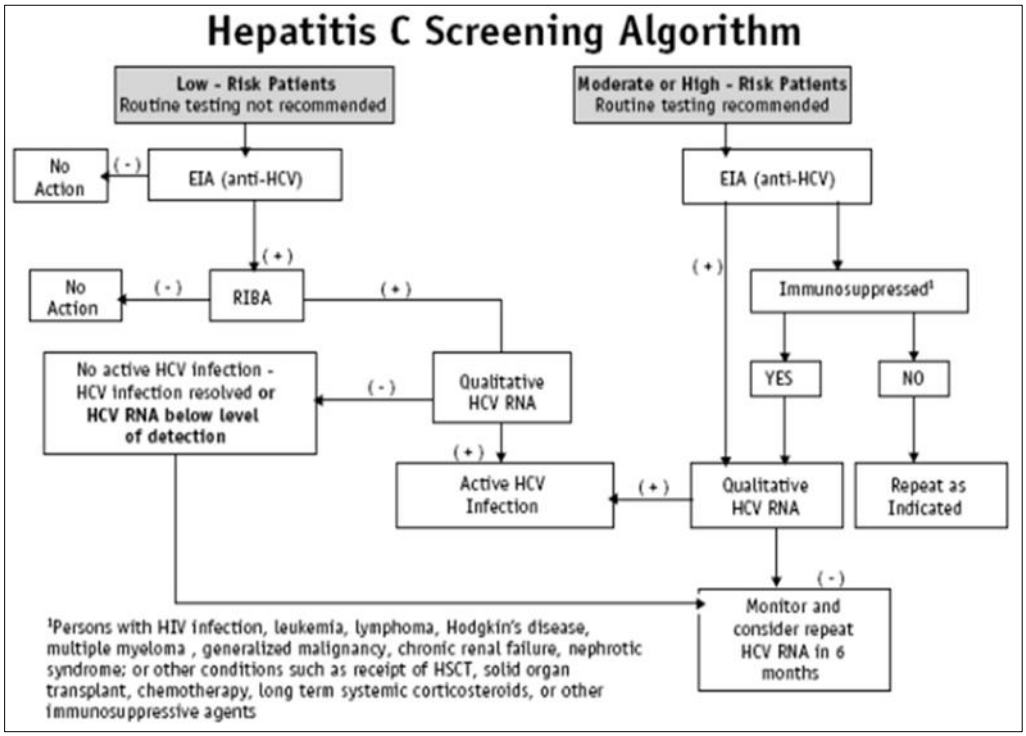

Figure 4 Steps of screening of HCV done in medical institutions

4. Conclusion

Hepatitis C is a chronic viral infection. primarily transmitted through blood-to-blood contact. The infection often progresses silently and can cause chronic liver disease like cirrhosis, and liver cancer after 15-20 years of progression. with a significant proportion of individuals remaining asymptomatic until significant liver damage occurs.

With the advent of DAA therapy, Hepatitis C is now highly treatable, and cure rates have drastically improved. In Early-stage diagnosis and cure can be helpful to prevent long-term complications such as cirrhosis and carcinoma. Prevention remains key, as there is no vaccine for HCV in world currently. rently with emphasis placed on screening, safe blood practices, and needle exchange programs. Regular monitoring and follow-up care ensure the best results for patients living with Hepatitis C.

Review

This article covers majority of the aspects related to the HCV, epidemiology and prevalence of HCV, transmission, signs and its symptoms, its diagnosis and screening algorithms, prevention, and its treatment. It also includes prophylaxis and prognosis of its treatment. For prognosis I have added some datas from various sources and it is quite helpful for understanding prognosis and outcome of the disease. Result and discussion is very detailed for understanding the screening algorithm of disease, Mortality rate graph is also useful and the Map that shows prevalence of the disease is a better way to learn epidemiology and Genotype vise prevalence of Hepatitis C virus. In conclusion I have summarised the whole article and their details conclusion of all aspects.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest in any of the statements present in the article.

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