LUMEN ET VIRTUS
ISSN: 2177-2789

CHRONIC HEPATITIS C VIRUS INFECTION: SYSTEMATIC REVIEW ON EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT OF THE CONDITION

https://doi.org/10.56238/levv16n44-024

Submission date: 12/13/2024 **Publication date:** 01/13/2025

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ABSTRACT

Objective: The general objective of this study is to analyze the scientific production of chronic infection by the Hepatitis C virus, seeking to identify the main methods used in the treatment of this pathology. Methodology: This is a systematic review focused on understanding the main aspects that permeate chronic infection by the Hepatitis C virus. The research was guided by the question: "What are the main aspects that permeate chronic infection by the Hepatitis C virus, as well as what are the diagnostic and therapeutic resources used in clinical practice?" To find answers, searches were performed in the PubMed database using four descriptors combined with the Boolean term "AND". This resulted in 542 articles. Nineteen articles were selected for analysis and 11 articles were used to compose the collection. Results: Hepatitis C is a viral infection that affects approximately 200 million people globally, causing serious complications such as liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Despite significant advances with the introduction of direct-acting antiviral agents (DAAs), which have high cure rates (>95%), barriers such as limited access to diagnosis, high drug costs, and stigma associated with substance use disorder hinder disease elimination. Conclusion: Solutions such as the use of generic drugs and decentralized care strategies are essential to overcome these barriers and reduce the global burden of hepatitis C.

Keywords: Chronic Hepatitis C. Treatment. Diagnosis.

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INTRODUCTION

The global prevalence of hepatitis C virus (HCV) is high, with recent estimates ranging from 57 million to 71 million people living with HCV. Marginalized populations, including people experiencing homelessness or housing instability, people in marginalized racial and ethnic groups, people with current or past involvement in the justice system, and particularly people who inject drugs (PWID), are disproportionately affected by HCV. In the US, more than 80% of HCV infections have been associated with injection drug use, and increases in HCV incidence have paralleled the opioid epidemic in recent years (MORRIS et al., 2023). The World Health Organization (WHO) has set a target of reducing new HCV infections by 90% and deaths by 65% by 2030. Although the global incidence of HCC has declined from 71 million to 56.8 million, only 11 countries are currently on track to meet the WHO 2030 elimination target. Virological cure significantly reduces liver-related complications and improves survival in patients with HCC (Devan et al., 2023). Hepatitis C virus (HCV) is a single-stranded RNA virus transmitted to humans primarily by direct inoculation into the blood or traumatic percutaneous exposure. Approximately 25% to 30% of individuals with acute infection spontaneously clear the virus within 6 to 12 months after infection, while the majority progress to develop chronic HCV infection, after which spontaneous clearance is extremely rare. Unlike chronic HCV, which can cause progressive liver damage, ultimately leading to cirrhosis, transient HCV infection is not associated with persistent liver injury or fibrosis. In patients with chronic infection who progress to cirrhosis, there is an increased risk of hepatocellular carcinoma (HCC), which is reduced but not eliminated with treatment-induced sustained virologic response (SVR) (HSU et al., 2023). Despite the high burden of disease caused by HCV and increased global awareness of the problem, many people living with HCV remain undiagnosed and therefore untreated. Efforts to offer testing more widely and frequently are a crucial first step towards scaling up treatment. To this end, emergency departments (EDs) have been identified as key settings for offering HCV testing to individuals who would otherwise not interact with healthcare systems or would not be offered HCV testing (ROWAN et al., 2023). Direct-acting antivirals (DAAs) have made widespread treatment of hepatitis C infection a viable strategy. With high cure rates and proven efficacy in multiple populations, DAAs are an attractive approach to controlling this global epidemic and its increasing financial burden on acute care systems (NG et al., 2024).

This systematic review aims to compile and evaluate the existing scientific evidence on chronic hepatitis C infection. The intention is to provide a comprehensive and up-to-date overview that not only synthesizes current knowledge about the condition but also identifies

research gaps and guides future investigations and clinical practices. By offering an in-depth analysis of the evidence, this work aims to serve as a resource for health professionals, researchers, and academics, helping to optimize diagnostic and therapeutic approaches for this condition.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of chronic hepatitis C infection, as well as demonstrate the main pharmacological methods used in the treatment of the condition. To develop this research, a guiding question was developed using the PVO strategy (population, variable, and objective): “What are the main aspects that permeate chronic infection by the Hepatitis C virus, as well as what are the diagnostic and therapeutic resources used in clinical practice?”

The searches were carried out through searches in the PubMed Central (PMC) databases. Four descriptors were used in combination with the Boolean term “AND”: Diagnosis, Hepatitis C, Treatment, and Signs and Symptoms. The search strategy used in the PMC database was: Diagnosis AND Hepatitis C, Hepatitis C AND Treatment, and Hepatitis C AND Signs and Symptoms. This search found 542 articles, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese, and Spanish; published between 2019 and 2024 that addressed the themes proposed for this research, in addition to review, observational, and experimental studies, made available in full. The exclusion criteria were: duplicate articles, made available in summary form, which did not directly address the proposal studied and which did not meet the other inclusion criteria.

After associating the descriptors used in the databases researched, a total of 408 articles were found. After applying the inclusion and exclusion criteria, 19 articles were selected from the PubMed database, with a total of 11 studies being used to compose the collection.

RESULTS

Cited Authors	Main Contributions to the Systematic Review
Ahmed et al.	200 million people globally are infected with HCV; infection induces hepatic fibrosis and cirrhosis, insulin resistance, steatosis, and hepatocellular carcinomas; treatment with DAAs is highly effective.
Hernandez-Con et al.	2.4 to 3.9 million people infected with HCV in the U.S.; increasing incidence among young people who inject drugs; DAAs revolutionized HCV treatment with high therapeutic efficacy and limited adverse events.
Burton; Voluse; Patel	Low HCV treatment rates among patients with substance use disorders; barriers to treatment include limited access to specialty care, especially in rural areas.

Tang et al.	In 2019, only 20% of people with HCV worldwide were aware of their status and 13% were treated; simplified service delivery models are needed to improve diagnosis and treatment rates.
Hsu et al.	HCV is associated with epigenetic changes in the host genome, increasing the expression of cancer-related genes; and persistent risk of HCC even after viral clearance.
Alberts et al.	The prevalence of viral infections in cirrhosis varies by region; HCV most common in Europe and the Americas; HBV most common in Africa and Asia.
Perazzo et al.	WHO strategies to eliminate HCV by 2030; substantial economic impact of DAAs; difficulties in achieving WHO targets due to new infections, lack of screening, and high costs.
Devan et al.	Virological cure reduces liver-related complications and improves survival; up to 5% of patients with HCC do not achieve SVR12 with DAAs; potential for generic drug versions for HCV eradication.
Morris et al.	Marginalized populations are disproportionately affected by HCV; over 80% of infections in the U.S. are associated with injecting drug use; HCV incidence corresponds to the opioid epidemic.
Rowan et al.	Many people living with HCV remain undiagnosed and untreated; emergency departments are identified as key settings for offering HCV testing.
Ng et al.	DAAs have made HCV infection treatment feasible; with high cure rates and proven efficacy in various populations; an attractive approach to control the global epidemic and reduce the financial burden on healthcare systems.

DISCUSSION

Hepatitis C is a serious health problem with a huge healthcare burden worldwide. Globally, 200 million individuals are currently infected with the hepatitis C virus (HCV), representing approximately 2–3% of the total global population. An estimated 3–4 million people are diagnosed with HCV annually. HCV infection induces liver fibrosis and cirrhosis. It also leads to several metabolic alterations such as insulin and interferon resistance, iron overload, steatosis, and the development of hepatocellular carcinomas with a high mortality rate (AHMED et al., 2020). In the USA alone, between 2.4 and 3.9 million people are infected with HCV, with an increasing incidence (approximately 40 per 100 person-years) among young people who inject drugs (PWIDs) and with approximately 50% of individuals unaware of their infection status. The incidence of HCV is also higher among PWID in other developed countries: in Australia, the incidence ranges from 7.6 to 12.8 per 100 person-years, while the incidence in England is 8.7 per 100 person-years. In 2013, the advent of oral direct-acting antiviral agents (DAAs) revolutionized the treatment of HCV infection. These new agents target different structures involved in the HCV replication process (e.g., they inhibit units of the replicase complex or ribonucleic acid (RNA) polymerase chain; they have 95% or greater therapeutic efficacy and limited adverse events, which has transformed HCV infection into a curable disease (HERNANDEZ-CON et al., 2023). This epidemic of hepatitis C infection is fueled by a concurrent epidemic of substance use disorders (SUDs), particularly opioid use disorders in predominantly rural settings. Although HCV is easily cured with a short and well-tolerated course of direct-acting antivirals (DAAs),

HCV treatment rates remain low among patients with SUDs. Barriers to HCV treatment among patients with SUDs include limited access to subspecialty care, which is amplified by the shortage of health care in rural areas and provider misperceptions about the reduced efficacy of treatment in this subgroup (BURTON; VOLUSE; PATEL, 2024).

In 2019, only 20% of people living with HCV worldwide were aware of their HCV status, and 13% had been treated. Diagnosis rates are even lower in low-income countries, with only 8% of people living with HCV diagnosed in 2016, compared with 43% in high-income countries. Addressing this significant gap in testing and treatment to achieve WHO targets requires a substantial scale-up of testing and treatment with simplified, decentralized service delivery models and task shifting (TANG et al., 2022).

Chronic HCV infection is diagnosed in two stages, with an initial screening stage using HCV antibody serological tests to verify previous HCV exposure, and a confirmatory stage using laboratory-based HCV nucleic acid RNA tests or central antigen (HCVcAg) tests to determine the presence of active viremic HCV infection and the need for treatment. However, access to these laboratory assays is limited in many resource-limited settings. Lack of viral load confirmation means that many people with chronic HCV infections are never referred for care and treatment. Overall, point-of-care HCV RNA viral load assays are easier to use than laboratory-based NAT assays and may improve access to diagnosis of viremic HCV infections, followed by treatment and monitoring of treatment response. These point-of-care (PoC) devices are typically battery-operated and do not rely on continuous electricity to operate; in addition, they use reagents that do not require refrigeration and are stored at room temperature (TANG et al., 2022). Hepatitis C virus (HCV) is a single-stranded RNA virus transmitted to humans primarily by direct inoculation into the blood or traumatic percutaneous exposure. Approximately 25% to 30% of individuals with acute infection spontaneously clear the virus within 6 to 12 months of infection, while the majority progress to develop chronic HCV infection, after which spontaneous clearance is extremely rare. Unlike chronic HCV, which can cause progressive liver damage, ultimately leading to cirrhosis, transient HCV infection is not associated with persistent liver injury or fibrosis. In patients with chronic infection who progress to cirrhosis, there is an increased risk of hepatocellular carcinoma (HCC), which is reduced but not eliminated with treatment-induced sustained virologic response (SVR). There is no known risk of HCC after spontaneous resolution of acute HCV; however, data are limited. Recent studies showed that HCV infection is associated with epigenetic alterations in the host genome, leading to increased expression of cancer-related genes that persist even after viral clearance. These epigenetic alterations were present in both acute and chronic infections; they were

demonstrated in patients with chronic HCV infections (most with significant fibrosis or F2-F4 fibrosis), but also in vitro cell culture studies after hepatoma cell lines were briefly infected for 1–2 weeks and in primary human hepatocytes after shorter durations of infections (HSU et al., 2023). Epigenetic alterations similar to those observed in cell culture were present in an 8-gene risk set associated with HCC in 7 liver biopsy specimens from patients with chronic active HCV infection and were also present in 4 liver biopsy specimens from patients cured of HCV with direct-acting antivirals (DAAs), raising concerns that HCV infection may lead to a persistent change in cells that may predispose to cancer. However, it is notable that HCV-related HCC occurs almost exclusively in patients with cirrhosis. Epigenetic alterations may lead to pathways involved in hepatocarcinogenesis. Several risk factors are associated with the development of HCC in patients with chronic HCV that persist even after achieving SVR. Advanced liver fibrosis or cirrhosis is by far the strongest risk factor for HCC, but other factors have also been identified, including previous exposure to hepatitis B virus (HBV), iron overload, fatty liver disease, autoimmune liver disease, type 2 diabetes, obesity, hypertension, and tobacco and alcohol use (HSU et al., 2023).

Although the prevalence of viral infections in cirrhosis varied from country to country, the contribution of HCV was generally highest in countries in the European and American regions, and the combined contribution of the two viruses in patients with cirrhosis was generally less than 50%. In contrast, in countries in the African and Asian regions, HBV was more common (although with some exceptions), and the combined prevalence of both viruses among patients with cirrhosis generally exceeded 50% (ALBERTS et al., 2022).

In the past decades, the recommended treatment for hepatitis C infection was a combination therapy of PEGy-sided interferon (PEG-IFN) and ribavirin (RBV) for 48 weeks. This combination was not effective enough for the eradication of HCV infection and was reported to suppress the infection by only 45-50% with vigorous side effects. Currently, HCV treatment has evolved rapidly, which led to the development of direct-acting antiviral agents (DAAs) for PEG-IFN-free antiviral regimens. This has led to a remarkable increase in sustained virologic response (SVR) rates (<90%) opening therapeutic options for patients with contraindications or low SVR rates using PEG-IFN-based antiviral therapy regimens (AHMED et al., 2020). Sofosbuvir (SOF) is a direct-acting antiviral agent developed as an oral treatment for hepatitis C infection. It is a nucleotide analog that inhibits the polymerase enzyme that plays a key role in RNA replication. Due to its structural similarity to a nucleotide, it competes with nucleotide features, and thus, by blocking the target site, it ultimately terminates viral replication within the host cell. RBV is also a guanosine nucleoside analog and exhibits antiviral activity against both RNA and DNA viruses. It has

been the mainstay of HCV regimens for hepatitis C infection over the past two decades. In the IFN-free period of hepatitis C treatment, ribavirin still exhibits a significant position in the most favorable treatment of several subgroups of difficult-to-cure diseases. HCV-infected patients. It increases the SVR rate and enhances the efficacy of PEG-IFN when used in combination with other DAAs (AHMED et al., 2020). SVR, SOF, and RBV drugs have adverse side effects including oxidative stress, which encourage us to explore new therapeutics and/or adjuvant therapies with a safer and more effective profile. Several options are available to control the adverse effects of antiviral drugs and to maintain liver protection, which may include natural agents and/or organic synthetic agents. A combination of ASC and BLC was used as adjuvant therapy in this study. ASC (vitamin C analogue) is abundant in various products. It stipulates remarkable antiviral, anticancer, anti-inflammatory, important antioxidant, and immunoregulatory effects. ASC has been reported to enhance the constituents of the human immune system such as lymphocyte proliferation, natural killer cell activity, chemotaxis, and hypersensitivity. It plays an important role in maintaining the balance between the oxidant and antioxidant systems of the human body. ASC has direct antioxidant potential and is involved in the protection of reactive nitrogen species and antioxidant oxygen radicals during immune activation (AHMED et al., 2020).

In 2016, the World Health Organization (WHO) outlined strategies to eliminate HCV infection and reduce the number of deaths related to viral hepatitis by 65% by 2030. However, the use of direct-acting agents has had a substantial economic impact in several countries due to high drug costs. However, adopting a test-and-treat strategy is cost-effective and is essential to achieving global treatment goals. Access to direct-acting agents varies widely across the world. 10 Several countries have provided access with minimal copayments or negotiated large discounts with the pharmaceutical industry to provide universal treatment for everyone living with HCV. Despite the availability of highly effective therapeutic regimens, however, the WHO target of eliminating HCV infection by 2030 will likely be difficult to achieve for several reasons, including the high rate of new infections; HCV-infected individuals remaining untreated due to lack of screening; patent restrictions affecting generic drugs; and the high price of direct-acting agents in middle-income countries with large HCV epidemics (Perazzo et al., 2020). Although the global incidence of HCC has declined from 71 million to 56.8 million, only 11 countries are currently on track to meet the WHO 2030 elimination target. Virologic cure significantly reduces liver-related complications and improves survival in patients with HCC. The direct-acting antiviral (DAA) based on sofosbuvir has been shown to achieve high SVR12 in real-world settings, even

among patients with HCV genotype 3. Although the introduction of highly effective DAA drugs has revolutionized the treatment of HCC, up to 5% of HCC patients still fail to achieve a sustained virological response at week 12 (SVR12) using DAAs (DEVAN et al., 2023). Generic versions of direct-acting agents can be provided at a much lower cost than branded drugs and may contribute to eradicating HCV infection in the coming years. Ideally, generic HCV direct-acting agents should be prequalified by the WHO (PERAZZO et al., 2020).

CONCLUSION

Hepatitis C remains a significant public health problem with high morbidity and mortality rates, especially in vulnerable populations. The introduction of direct-acting antivirals (DAAs) has revolutionized treatment, offering cure rates of over 95% and fewer adverse events compared to interferon-based therapies. However, challenges such as limited access to diagnosis and treatment, especially in low- and middle-income countries, continue to hamper global efforts to eliminate the virus. Despite important advances, such as the availability of generic drugs and universal testing and treatment strategies, the WHO goal of eliminating hepatitis C by 2030 faces significant barriers, including high rates of reinfection, and gaps in early diagnosis and management of patients with co-existing conditions such as substance use disorders. Furthermore, long-term complications, such as hepatocarcinogenesis associated with chronic HCV, highlight the need for continued monitoring even after sustained virological response. Strengthening decentralized models of care, expanding testing, and reducing drug costs are essential to achieve greater equity in treatment and ultimately eliminate the global burden of this infection.

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