RJNMSR
Review Journal of Neurological & Medical Sciences Review
Volume 3, Issue 4, 2025

AWARENESS AND KNOWLEDGE GAPS IN VIRAL HEPATITIS B AND C: A PUBLIC HEALTH PERSPECTIVE

Sabira Sultana[1], Rizwana Dilshad[2], Rabia Nisar[3], Aqsa Afzal[4], Maqsood Ahmad[5], Rimsha Zainab[6], Fethi Ahmet Ozdemir[7], Gawel Solowski[8], Shafqat Rasool[9], Iftikhar Younis Mallhi[10], Muhammad Mudassar[11], Mohsin Rafique[12], Muhammad Akram[13*]

[1]*Department of Eastern Medicine Government College University Faisalabad-Pakistan*
[2]*Swedish College of Pharmacy and Allied Health Sciences, Rahim Yar Khan, Pakistan*
[3]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The Islamia University of Bahawalpur, Punjab, Pakistan*
[4]*Faculty of Pharmacy, Department of Pharmaceutics, Bahauddin Zakaria University Multan*
[5]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, The Islamia University of Bahawalpur, 63100, Bahawalpur, Pakistan*
[6]*Department of Botany, Shaheed Benazir Bhutto Women University, Peshawar, Pakistan*
[7]*Department of Molecular Biology and Genetics, Faculty of Science and Art, Bingol University, Bingol, 12000, Türkiye*
[8]*Department of Molecular Biology and Genetics, Faculty of Science and Art, Bingol University, Bingol, 12000, Türkiye*
[9]*School of Eastern Medicine, Minhaj University Lahore, Pakistan*
[10]*School of Human Nutrition and Dietetics, Minhaj University Lahore, Pakistan*
[11]*College of Allied Health Sciences, Faculty of medical sciences, Government College University Faisalabad, Pakistan*
[12]*Department of Eastern Medicine, Superior University Lahore, Pakistan*
[*13]*Department of Eastern Medicine, Government College University Faisalabad Pakistan*
[*14]muhammadakram@gcuf.edu.pk

Corresponding Authors: *
Muhammad Akram

DOI: https://doi.org/

Received	Accepted	Published
26 July, 2025	27 Aug, 2025	29 Aug, 2025

ABSTRACT

Treatment of acute hepatitis B within the first 24 months is generally unnecessary, as approximately 90% of infections in adults resolve spontaneously, with or without treatment. In the early stages, medical intervention plays only a limited role, though in rare cases, antibiotics may be beneficial for severe inflammation. Chronic hepatitis B treatment strategies include interferon therapy and nucleoside/nucleotide analogues. Interferon therapy, typically administered over 24–48 weeks, is associated with adverse effects such as fatigue, depression, alopecia, and hematological abnormalities, with optimal outcomes observed in patients exhibiting elevated transaminases, absence of cirrhosis, and hepatitis B e-antigen positivity. Although many remain asymptomatic, long-term infection carries significant clinical and financial burdens. Estimated early healthcare costs for children with CHC in the United States to exceed $200 million. Complementary and herbal approaches have also been explored. Similarly, silymarin (a flavonoid extract from milk thistle) has shown promise in difficult-to-treat hepatitis cases. . Although most participants demonstrated awareness of hepatitis B and C, misconceptions remained regarding transmission modes. Finally, phytochemical evaluations confirmed that phenolic compounds contribute significantly to the hepatoprotective activity of many traditional medicinal plants.

Keywords: *Hepatitis, Medicinal Plants, Pakistan, Epidemiology*

INTRODUCTION

The hepatic system is involved in nearly all biochemical pathways essential for human development, immune response, complement activation, and energy metabolism. Both infectious and non-infectious pathological processes can compromise hepatic function (Mohon et al., 2014). Hepatic pathology represents a substantial burden on international health systems, with hepatitis B and C viral infections comprising predominant and preventable causes of liver-related morbidity (Mishra et al., 2014).

Ethnobotany encompasses the systematic study of relationships between human populations and plant species (Ijaz et al., 2017). Throughout human civilization, medicinal plants have been utilized for their therapeutic properties. Currently, approximately 80% of the global population relies predominantly on plant-based remedies and botanical extracts for primary healthcare needs. Numerous medicinal plants and their derived compounds have demonstrated hepatoprotective properties (Thilagavathi et al., 2023). Consequently, there exists a substantial risk that traditional medicinal knowledge may be irretrievably lost, necessitating urgent conservation efforts to preserve this valuable therapeutic heritage.

Hepatitis-B virus (HBV)

The risk of HBeAg seroconversion in adolescents is higher for genotype C compared to other genotypes (Livingston et al., 2007). During the mid-1990s, the United States experienced a reduction in acute hepatitis B virus infections (Goldstein et al., 2002; Chan et al., 2004).

Diagnosis and Tests

Anti-HBc IgM represents the initial immune response marker, persisting throughout the acute phase. During the serological window period characterized by anti-HBc IgM positivity, HBsAg becomes undetectable while antibodies to hepatitis B surface antigen (anti-HBs) emerge, indicating viral clearance and immunity development.

An increase in HBV-specific IgG antibodies in individuals exposed to significant HBV infection is encouraging. The emergence of antibodies to hepatitis B e antigen (anti-HBe) signifies seroconversion, accompanied by subsequent reduction in circulating HBV DNA concentrations. Progressive temporal changes result in diminished HBeAg detectability as the infection transitions toward immune control. Measuring HBsAg in those who have tested positive for HBV for more than six months revealed that there is an HBV carrier or an improvement in the condition of having HBV.

Young people infected via maternal-embryonic transmission may remain at this stage for several years and are less responsive to antiviral drugs, which have shown varying efficacy in different studies. The immune-active phase of chronic hepatitis B is characterized by elevated serum aminotransferases (ALT > 1.6 times the upper limit of normal on multiple occasions) and persistent viral replication (HBV DNA > 20,000 IU/mL or 10^5 copies/mL), with positive HBsAg and HBeAg serological markers. This phase represents the optimal period for HBeAg seroconversion in pediatric patients and demonstrates enhanced responsiveness to antiviral therapeutic interventions.

The non-replicative or inert HBeAg stage is described in the literature as sedentary CHB stages. The inactive carrier state is characterized by positive HBsAg with negative HBeAg serological markers. Approximately 20% of adolescents in this non-replicative phase experience reversion to the immune-active state, while 20-30% develops HBeAg-negative chronic hepatitis B with renewed viral activity (Hsu et al., 2002).

Hepatitis B Prevention and Treatment

Comprehensive hepatitis B management in children integrates prevention protocols, therapeutic interventions, and vaccination programs designed to minimize viral transmission and halt disease progression. The prevention of vertical transmission is primarily based on a combined approach of passive-active immunization, which involves administering hepatitis B immunoglobulin (HBIG) along with the hepatitis B vaccine. This combined strategy achieves prevention rates of 86-96%, compared to 66-96% for vaccination alone (Wong et al., 1984). Contemporary treatment paradigms for pediatric chronic hepatitis B emphasize viral replication control, hepatic inflammation amelioration, and prevention of cirrhotic progression and hepatocellular carcinoma development, with established FDA-approved regimens including thrice-weekly interferon alpha and daily lamivudine therapy administered over 16-24 weeks in patients aged 2-18 years (Sokal et al., 2008), although lamivudine resistance develops in approximately 20% of treated patients per year (Hu et al., 2025). Expanded therapeutic options now include tenofovir disoproxil fumarate approval for adolescents 12 years and older (Murray et al., 2012) and entecavir authorization based on phase 3 efficacy data in treatment-naive pediatric cohorts aged 2-18 years, while nucleoside analogue therapy carries regulatory warnings for mitochondrial dysfunction, with documented adverse effects encompassing lamivudine-associated myopathy and peripheral neuropathy, adefovir and tenofovir-related nephrotoxicity, and potential pancreatitis risk (Khungar et al., 2010). Established immunization protocols mandate combined HBIG and hepatitis B vaccination within 12 hours of delivery for neonates born to HBsAg-positive mothers (ACIP, 1991), generating protective anti-HBs antibody concentrations above 10 mIU/mL in approximately 95% of vaccinated children. Although vaccine-elicited immunity wanes over time, necessitating booster doses for primary non-responders (Hennig et al., 2008). Current guidelines from the American Association for the Study of Liver Diseases support antiviral intervention during pregnancy for high-viremia patients to minimize perinatal transmission risk. Emerging vaccine technologies incorporating PGLYRP2 protein platforms demonstrate potential for improved immunogenicity and protection (Zeng et al., 2015; Li et al., 2025).

Special Considerations

As the disease progresses, the technique for obtaining the trait or the potential of the Hepatitis B (Hep-B) virus based on the usual course of chronic Hep-B in teenagers remains unpredictable. Routine hepatitis B virus genotype determination is not standard clinical practice; however, genotyping may provide therapeutic guidance for HBeAg-positive pediatric patients under consideration for interferon-based treatment. Enhanced interferon responsiveness has been documented in patients infected with genotypes A and B compared to genotype C infections. Hepatitis B virus genotype may influence hepatocellular carcinoma risk in younger populations relative to adult cohorts. Key risk factors for hepatocellular carcinoma development in pediatric patients include disease severity, histological inflammation grade, and active viral replication status as measured by HBV DNA concentrations.

Hepatocellular carcinoma can still occur after viral replication has stopped or before the HBeAg seroconversion time (Wen et al., 2004). Screening for HCC in youths is challenging. Research on hepatocellular carcinoma (HCC) in adults with hepatitis B virus indicates that monitoring liver health through regular ultrasounds and measuring serum alpha-fetoprotein (AFP) levels can be beneficial, with more frequent checks recommended for those with elevated AFP, cirrhosis, or a family history of HCC(EASL-EORTC, 2012).

The economic impact of chronic hepatitis B (CHB) in adolescents is considerable, driven by environmental factors such as pollution and the associated risks of cirrhosis and hepatocellular carcinoma (HCC). Mitigating this burden requires antiviral treatments that target the virus's replication cycle, rather than focusing solely on managing the symptoms of viral activity. Acute hepatitis increased by 19% from 1990 worldwide, with a huge increase of 25% in sub-Saharan men aged between 55 and 59 years old (Ouyang et al., 2024). Efforts have also focused on finding average, effective, and successful elective solutions for antiviral therapy.

In recent decades, both clinical and preclinical studies have suggested that certain Chinese herbal medicines may offer therapeutic benefits in two or three treatment approaches for chronic hepatitis B (CHB). However, concerns arise regarding the evaluation of basic clinical principles and the unique and contradictory fixing components of Chinese medicines in daily practice (Zhang et al., 2010; Wang et al., 2012).

HCV Epidemiology and Expected Antiquity

Hepatitis C virus (HCV) infection represents a major global health burden, affecting an estimated 170 million individuals worldwide. In the United States alone, approximately seven million adults and around 100,000 children are thought to be infected (Jonas, 2003). Data from the Third National Health and Nutrition Examination Survey estimated a seroprevalence of 0.2–0.4% among children, corresponding to about 132,000 HCV antibody–positive cases (Alter et al., 1994). Of these, 23,000 to 42,000 children were chronically infected, with an additional 7,200 new pediatric cases occurring annually (Jhaveri et al., 2006). In the United States, the most common circulating hepatitis B virus strains are genotypes 1a and 1b, followed by genotypes 2 and 3, while genotypes 4 through 6 are reported less frequently (Luban et al., 2007). Before 1992, most pediatric infections were linked to contaminated blood transfusions or blood-derived products, with an estimated risk of 0.001–0.01% per unit transfused (Luban et al., 2007). In the post-screening era, vertical transmission has become the leading route of new pediatric infections (Jhaveri et al., 2006; Granot et al., 2015). United States data demonstrate that 57.3% of perinatally infected infants clear HCV by age three, rising to 65.9% by age five, highlighting the critical importance of early screening and follow-up protocols (Voeller et al., 2025). According to Mock et al. (2005), only about one-third of infants born to HCV-infected mothers acquire the virus in utero. Additionally, HCV has been identified in breast milk (Lin et al., 1995) and colostrum (Kumar & Shahul, 1998). HCV transmission rates were elevated in young infants who were exposed to breast milk containing HCV RNA (Ruiz-Extremera et al., 2000). Majority evaluations have not shown a relationship between transmission and the treatment method (Granovsky et al., 1998; Resti et al., 1998). Unlike the hepatitis B virus, children infected with HCV exhibit a higher likelihood of spontaneous viral clearance.

Approximately 25–40% of infants who acquired HCV through vertical transmission show undetectable HCV RNA levels by the age of 2–3 years (Resti et al., 2003a), while 6-12% of children near 7 years had an undetectable HCV RNA level (Resti et al., 2003b; Yeung et al., 2008). A more plausible undetectable viral load occurred with genotype 3 HCV disease. (Bortolotti et al., 2008; Chen et al., 2009) reported that among 42 adolescents with persistent HCV infection and baseline RNA levels below 4.5×10^4 IU/mL, a high proportion achieved undetectable viral loads..

However, adolescents who contracted HCV through parenteral transmission surprisingly had a viral load that remained detectable. In up to 30 years of longitudinal follow-up, viral load reached 11% (Casiraghi et al., 2004) and 30-45% in a study of infants' contaminatedwith a positive blood product for HCV RNA (Vogt et al., 1999) or infected blood products in clinical practice separately (Locasciulli et al., 1997). Adolescents presenting with elevated serum aminotransferase levels at disease onset were more likely to experience significant biochemical improvement

(Resti et al., 2003b), and the appearance of viraemia differed compared to those with normal serum aminotransferases (Farmand et al., 2012). Clinical presentation of pediatric HCV infection varies significantly, with approximately 80% of infected children remaining asymptomatic due to consistently elevated viral activity (Gan et al., 2025), while 10-20% present with overt signs and symptoms of hepatic dysfunction, and progression to an elevated aspartate aminotransferase to alanine aminotransferase ratio (AST>ALT) may indicate cirrhotic transformation in chronic hepatitis C patients (Schwarz et al., 2011). While cirrhosis occurs in only 1–2% of children with HCV infection, progression to end-stage liver disease generally takes 20–40 years. Rare cases of hepatocellular carcinoma have been reported in adolescents, including a 14-year-old African American patient with genotype 1a infection who developed terminal liver disease. In this case, alpha-fetoprotein levels rose from 7.9 to 76.6 ng/mL over four months, ultimately necessitating hepatectomy for solitary hepatic lesions (Alter et al., 2000; Gonzalez-Peralta et al., 2009). Patients who achieve a sustained virological response have a markedly lower risk of hepatocellular carcinoma compared to those who do not clear the virus, highlighting the critical role of antiviral therapy in suitable candidates (Nishiguchi et al., 1995, 2001).

Diagnostic Tests

Diagnostic approaches for hepatitis C virus infection follow established guidelines from the American Association for the Study of Liver Diseases (2009) and the Centers for Disease Control and Prevention (2013), with screening recommended for adolescents and young adults with clinical histories of hepatitis, unexplained serum aminotransferase elevation, HIV coinfection, intravenous drug use, sexual assault, multiple sexual partners, or maternal HCV infection, as well as children adopted internationally or refugees from regions with high HCV prevalence, such as Africa, Eastern Europe, Russia, China, and Southeast Asia (Ghany et al., 2009; CDC, 2013; American Academy of Pediatrics, 2015). After obtaining positive or indeterminate HCV antibody results, HCV RNA testing is recommended to confirm chronic infection, since the presence of RNA indicates ongoing viral replication (Ghany et al., 2009). In infants born to HCV-positive mothers, maternal antibodies can remain for up to 18 months, making HCV antibody testing at 18 months necessary to differentiate between passively acquired antibodies and actual infection (American Academy of Pediatrics, 1998). A reactive HCV antibody test without detectable RNA may reflect either spontaneous viral clearance or a resolved infection. False-negative antibody results can occur in immunocompromised individuals, such as those with advanced HIV, hemodialysis patients, or transplant recipients. Therefore, concurrent HCV RNA testing is necessary for accurate diagnosis, as viral RNA can be detected within 10–14 days after infection.

Prevention and Treatment

Adolescents and young adults need to be vaccinated against hepatitis A and hepatitis B, but effective vaccination rates remain low. The incidence of chronic hepatitis C virus (HCV) disease in more settled children and adolescents revolves around the organization of high-risk practices. Risk factors include sexual activity with multiple partners, intravenous drug use, and intranasal cocaine use involving shared equipment. While tattooing and body piercing are not inherently linked to HCV transmission, the use of shared or non-sterile needles for these practices should be avoided (Murray et al., 2003). The primary goal of HCV therapy is to achieve a sustained virologic response (SVR), defined as the absence of detectable HCV RNA in peripheral blood 24 weeks after completing treatment. Although loss of SVR may occur in rare cases, studies demonstrate that more than

99% of patients who reach SVR maintain undetectable serum HCV RNA (Nelson et al., 2009).

The treatment of pediatric HCV infection has largely followed the same clinical guidelines established for adults. Early clinical studies in adolescents have examined the efficacy and safety of these agents. In limited, uncontrolled trials of stepwise triple interferon therapy, SVR rates in young patients ranged from 30–60%, notably higher than the 8–35% observed in adults (Jackobson et al., 2002).

In a study evaluating delayed-response interferon following either the initial dose or one week after pegylated interferon alfa-2a (PEG-IFNα-2a), children aged 2–8 years with HCV achieved an overall SVR rate of 43%, including 46% among those with genotype 1 (Schwarzet al., 2006). In 2025, pegylated interferon became the initial treatment procedure (Zhou et al., 2025). An open-label trial assessing PEG-IFNα-2b in combination with oral ribavirin (RV) in children and adolescents aged 2–17 years with HCV genotype 1 reported an SVR rate of 48%. Approval for pediatric use in the United States was granted on the basis of this single uncontrolled study (Wirth et al., 2005).

The standard FDA-approved treatment for chronic hepatitis C in children involves pegylated interferon alpha-2a or alpha-2b combined with ribavirin, administered for 24 weeks in patients with genotypes 2 and 3 and for 48 weeks in those with genotypes 1 and 4(Mack et al., 2012). The PEDS-C trial, a randomized, double-blind, placebo-controlled study, showed that adding ribavirin to pegylated interferon alpha-2a significantly improved sustained virological response compared to monotherapy, independent of age, aminotransferase levels, or histological severity, with the greatest benefit in children with chronic hepatitis C and HCV RNA <600,000 IU/mL(Schwarz et al., 2011). A systematic review and meta-analysis of eight trials including 438 children (aged 3–18 years) treated with pegylated interferon alpha-2a or alpha-2b plus ribavirin found genotype-specific outcomes: SVR rates were 89% for genotypes 2 and 3, compared to about 52% for genotypes 1 and 4(Druyts et al., 2013). Combination therapy yields sustained virological response rates approaching 100% in children with HCV genotypes 2 and 3, whereas those with genotypes 1 and 4 exhibit response rates of 45-55%Common side effects include general symptoms like flu-like illness, muscle pain, low white blood cell counts, anemia, and low platelet counts. More severe complications can arise, such as thyroid issues, hair loss, and neuropsychiatric effects, which may include changes in mood, irritability, anxiety, depression, and thoughts of suicide (Schwarz et al., 2011; Granot et al., 2015). Rare neurological complications, including spastic diplegia, have been reported in association with interferon alpha therapy in pediatric patients (Wörle et al., 1999; Jonas et al., 2012). The medications were also evaluated in pediatric trials, although for a limited time (Brown, 2009). Nevertheless, both were later withdrawn due to severe adverse effects, including telaprevir-associated rash and Stevens–Johnson syndrome and boceprevir-related dyspepsia. Current therapeutic strategies prioritize DAAs, which, owing to their high efficacy, form the cornerstone of the WHO's target to eliminate hepatitis C by 2030 (di Marco et al., 2025).

Treatment decisions for pediatric chronic hepatitis C must consider contraindications and patient-specific factors, as children who previously failed interferon-based therapy without achieving sustained virological response may still respond to pegylated interferon combined with ribavirin retreatment regimens. The broad range of adverse effects linked to pegylated interferon alpha-2a and ribavirin therapy can negatively impact treatment efficacy and tolerability, particularly in patients with advanced liver disease. Additionally, end-stage liver or kidney disease is typically considered an absolute contraindication for interferon-based treatments (Masci et al., 2003). The creation of new therapeutic agents that offer better safety profiles and increased efficacy marks a significant progress in the management of hepatitis C. Risk-benefit analysis suggests that children with HCV genotypes 2 and 3, youth patients with genotype 1 infection, and those with normal serum aminotransferases—who typically demonstrate milder hepatic pathology, higher spontaneous clearance rates, and reduced risk of cirrhosis and hepatocellular carcinoma progression—may benefit from deferring treatment until more effective antiviral therapies with fewer adverse effects become available. Promising results from phase II and III clinical trials with direct-acting antivirals beyond first-generation protease inhibitors, telaprevir and boceprevir in adult populations demonstrate significantly shorter treatment durations and higher sustained virological response rates. Modern combination therapies that incorporate NS3/4A protease inhibitors, such as simeprevir, alongside NS5B RNA polymerase inhibitors like sofosbuvir, have demonstrated improved response rates and shorter treatment durations. These therapies can be used with or without interferon alpha and ribavirin in patients with both treatment-experienced genotype 1 HCV- and naïve infections (Everson et al., 2014; Fried et al., 2013). These regimens demonstrate markedly improved tolerability profiles, with adverse effects limited primarily to mild constitutional symptoms including fatigue, depression, and nausea (Lawitz et al., 2014). Fixed-dose combination therapy with sofosbuvir and the NS5A inhibitor ledipasvir achieves sustained virological response rates of 95-100% in genotype 1 infections following 12 weeks of treatment, either as monotherapy or combined with 8-12 weeks of ribavirin in treatment-experienced adults or those with compensated cirrhosis (Gentile et al., 2014). As of September 2016, ten direct-acting antivirals (DAAs) have been granted regulatory approval and are organized into six therapeutic classes, targeting different HCV genotype-specific treatment algorithms. These therapeutic advancements are expected to establish new treatment paradigms for pediatric patients in the near future. Until DAAs receive pediatric approval, children with HCV infection should be managed using FDA-approved adult formulations only in cases of high-risk progressive liver disease. Concurrently, ongoing pharmacokinetic and safety studies are essential to establish appropriate pediatric dosing regimens. Emerging CRISPR-based technologies utilizing genomic analysis and historical clinical data offer potential for enhanced disease staging assessment and personalized treatment approaches (Adlat et al., 2025)

Special Deliberations and Arguments

Children with hepatocellular carcinoma (HCC) exhibit different transmission modes, viral load dynamics, and liver fibrosis progression compared to adults (Murray et al., 2005). It is generally believed that young individuals with vertical transmission of HCV face a risk of developing cirrhosis and HCC in adulthood. The advancements in hepatitis C treatment are ongoing, and direct-acting antivirals (DAAs) have emerged as highly effective cures, even for HCV-infected adults with compensated cirrhosis. The liver's histological condition prior to treatment does not significantly affect the treatment response. A DAA-based combination, consisting of sofosbuvir [400 mg] and ledipasvir [90 mg] in a single tablet, received approval for adult use in the United States in 2014, and clinical trials are currently underway to evaluate its tolerability and efficacy in children (Afdhal et al., 2014).

CONCLUSION

We compiled representative clinical data from the field of liver diseases to facilitate a comprehensive assessment. To establish a reliable dataset, pharmacodynamic information on the studied plant species was collected, with a focus on materials relevant to hepatoprotection. Preliminary phytochemical analysis revealed that phenolic compounds were at least partly responsible for the bioactivity of several extracts, particularly in their potential to inhibit malignant cell growth. However, these findings highlight the need for further validation through rigorous in vitro and in vivo studies to confirm both the efficacy and safety of the hepatoprotective effects.

REFERENCES

Adlat, S., Salgado, A. M. V., Lee, M., Yin, D., & Wangensteen, K. J. (2025). Emerging and potential use of CRISPR in human liver disease. Hepatology, 82(1), 232-253.

Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014; 370:1889–98. [PubMed: 24725239]

Alter HJ, Seeff LB. Recovery, persistence, and sequelae in hepatitis C virus infection: a perspective on long-term outcome. Semin Liver Dis. 2000; 20:17–35. [PubMed: 10895429]

Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med. 1999; 341:556–562. [PubMed: 10451460]

Bortolotti F, Cadrobbi P, Crivellaro C, et al. Long-term outcome of chronic type B hepatitis in patients who acquire hepatitis B virus infection in childhood. Gastroenterology. 1990; 99:805–10. [PubMed: 2379783]

Bortolotti F, Jara P, Crivellaro C, et al. Outcome of chronic hepatitis B in Caucasian children during a 20-year observation period. J Hepatol. 1998; 29:184–90. [PubMed: 9722198]

Bortolotti F, Verucchi G, Camma C, et al. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. Gastroenterology. 2008; 134:1900–7. [PubMed: 18439604]

Brown NA. Progress towards improving antiviral therapy for hepatitis C with hepatitis C virus polymerase inhibitors. Part I: Nucleoside analogues. Expert OpinInvestigDrugs. 2009; 18:709–725.

Casiraghi MA, De PM, Romano L, et al. Long-term outcome [35 years] of hepatitis C after acquisition of infection through mini transfusions of blood given at birth. Hepatology. 2004; 39:90–6. [PubMed: 14752827]

Centers for Disease Control and Prevention [CDC]. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013; 62:362. [PubMed: 23657112]

Chan HL, Hui AY, Wong ML, Tse AM, Hung LC, Wong VW, Sung JJ. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. Gut. 2004; 53:1494–8. [PubMed: 15361502]

Chen ST, Ni YH, Chen PJ, et al. Low viraemia at enrollment in children with chronic hepatitis C favours spontaneous viral clearance. J Viral Hepat. 2009; 16:796–801. [PubMed: 19413696

Di Marco, L., Cannova, S., Ferrigno, E., Landro, G., Nonni, R., Mantia, C. L., ... & Di Marco, V. (2025). A Comprehensive Review of Antiviral Therapy for Hepatitis C: The Long Journey from Interferon to Pan-Genotypic Direct-Acting Antivirals (DAAs). Viruses, 17(2), 163.

Druyts E, Thorlund K, Wu P, et al. Efficacy and safety of pegylated interferon alfa-2a or alfa-2b plus ribavirin for the treatment of chronic hepatitis C in children and adolescents: a systematic review and meta-analysis. Clin Infect Dis. 2013; 56:961–7. [PubMed: 23243171]

Euler GL, Wooten KG, Baughman AL, Williams WW. Hepatitis B surface antigen prevalence among pregnant women in urban areas: implications for testing, reporting, and preventing perinatal transmission. Pediatrics. 2003; 111:1192–7. [PubMed: 12728137]

European Association for Study of Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Eur J Cancer. 2012; 48:599–641. [PubMed: 22424278]

Everson G, Cooper C, Hezode C, et al. DAUPHINE: a randomized phase II study of danoprevir/ ritonavir plus peginterferon alpha-2a/ribavirin in HCV genotypes 1 or 4. Liver Int. 2014; 35:108–19. [PubMed: 24517252]

Farmand S, Wirth S, Loffler H, et al. Spontaneous clearance of hepatitis C virus in vertically infected children. Eur J Pediatr. 2012; 171:253–8. [PubMed: 21735055]

Fried MW, Buti M, Dore GJ, et al. Once-daily simeprevir [TMC435] with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. Hepatology. 2013; 58:1918–29. [PubMed: 23907700]

Gan, C., Yuan, Y., Shen, H., Gao, J., Kong, X., Che, Z., ... & Xiao, J. (2025). Liver diseases: epidemiology, causes, trends and predictions. *Signal Transduction and Targeted Therapy*, *10*(1), 33.

Gentile I, Buonomo AR, Zappulo E, et al. Interferon-free therapies for chronic hepatitis C: toward a hepatitis C virus-free world? Expert Rev Anti Infect Ther. 2014; 12:763–73. [PubMed: 24918116]

Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009; 49:1335. [PubMed: 19330875]

Goldstein ST, Alter MJ, Williams IT, et al. Incidence and risk factors for acute hepatitis B in the United States, 1982–1998: implications for vaccination programs. J Infect Dis. 2002; 185:713–9. [PubMed: 11920288]

González-Peralta RP, Langham MR Jr, Andres JM, Mohan P, Colombani PM, Alford MK, Schwarz KB. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. J Pediatr Gastroenterol Nutr. 2009; 48:630–5. [PubMed: 19412012]

Granot E, Sokal EM. Hepatitis C Virus in Children: Deferring Treatment in Expectation of Direct- Acting Antiviral Agents. Isr Med Assoc J. 2015; 17:707–11. [PubMed: 26757569]

Granovsky MO, Minkoff HL, Tess BH, et al. Hepatitis C virus infection in the mothers and infants cohort study. Pediatrics. 1998; 102:355–9. [PubMed: 9685438]

Hennig BJ, Fielding K, Broxholme J, et al. Host genetic factors and vaccine-induced immunity to hepatitis B virus infection. PLoS One. 2008; 26:3, e1898

Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology. 2002; 35:1522. [PubMed: 12029639]

Hu, Y., Zhang, Y., & Jiang, W. (2025). Targeting hepatitis B virus-associated nephropathy: efficacy and challenges of current antiviral treatments. *Clinical and Experimental Medicine*, *25*(1), 57.

Ijaz, F., Iqbal, Z., Rahman, I. U., Ali, N., & Afzal, M. (2017). People-plants interaction and its uses: a science of four words “ethnobotany”. *Altern Integr Med*, 6(1), 1-2.

Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011; 364:2405–16. [PubMed: 21696307]]

Khungar V, Han S. A Systematic Review of Side Effects of Nucleoside and Nucleotide Drugs Used for Treatment of Chronic Hepatitis B. Curr Hepatitis Rep. 2010; 9:75–90.

Kumar RM, Shahul S. Role of breastfeeding in transmission of hepatitis C virus to infants of

HCV- infected mothers. J Hepatol. 1998; 29:191–7. [PubMed: 9722199]

Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. Lancet. 2014; 384:1756–65. [PubMed: 25078309]

Li, Y., Ma, H., Zhang, Y., He, T., Li, B., Ren, H., ... & Shi, M. (2025). PGLYRP2 drives hepatocyte-intrinsic innate immunity by trapping and clearing hepatitis B virus. The Journal of Clinical Investigation, 135(8).

Livingston SE, Simonetti JP, Bulkow LR, et al. Clearance of hepatitis B e antigen in patients with chronic hepatitis B and genotypes A, B, C, D, and F. Gastroenterology. 2007; 133:1452–7. [PubMed: 17920063]

Locasciulli A, Testa M, Pontisso P, et al. Prevalence and natural history of hepatitis C infection in patients cured of childhood leukemia. Blood. 1997; 90:4628–33. [PubMed: 9373275]

ltayeb AA, Abdou MA, Abdel-aal AM, Othman MH. Vitamin D status and viral response to therapy in hepatitis C infected children. World J Gastroenterol. 2015; 21:1284–91. [PubMed: 25632203]

Luban NL, Colvin CA, Mohan P, Alter HJ. The epidemiology of transfusion-associated hepatitis C in a children's hospital. Transfusion. 2007; 47:615–620. [PubMed: 17381619]

Masci P, Bukowski RM, Patten PA, Osborn BL, Borden EC. New and modified IFN alfas: preclinical and clinical data. Curr Oncol Rep. 2003; 5:108–113. [PubMed: 12583827]

Mishra, P., Florian, J., Qi, K., Zeng, W., Naeger, L. K., Donaldson, E., ... &Birnkrant, D. (2014). FDA perspective on sofosbuvir therapy for patients with chronic hepatitis C virus genotype 1 infection who did not respond to treatment with pegylated interferon and ribavirin. *Gastroenterology*, *147*(6), 1196-1200.

Mohan G. Kalaskar and Sanjay J. Surana, 2014. Ethnomedicinal Plants used Against Liver Diseases among the Tribes of India: Review. *Journal of Biological Sciences, 14: 154-168.*

Mok J, Pembrey L, Tovo PA, Newell ML. European Paediatric Hepatitis C Virus Network. When does mother to child transmission of hepatitis C virus occur? Arch Dis Child Fetal Neonatal Ed. 2005; 90:F156–60. [PubMed: 15724041]

Murray KF, Finn LS, Taylor SL, Seidel KD, Larson AM. Liver histology and alanine aminotransferase levels in children and adults with chronic hepatitis C infection. J Pediatr Gastroenterol Nutr. 2005; 41:634–8. [PubMed: 16254522]

Murray KF, Richardson LP, Morishima C, Owens JW, Gretch DR. Prevalence of hepatitis C virus infection and risk factors in an incarcerated juvenile population: a pilot study. Pediatrics. 2003; 111:153. [PubMed: 12509569]

Murray KF, Szenborn L, Wysocki J, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. Hepatology. 2012; 56:2018–26. [PubMed: 22544804]

Nainan OV, Alter MJ, Kruszon-Moran D, Gao FX, Xia G, McQuillan G, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. Gastroenterology. 2006; 131:478–484. [PubMed: 16890602]

Nelson DR, Davis GL, Jacobson I, et al. Hepatitis C virus: a critical appraisal of approaches to therapy. Clin Gastroenterol Hepatol. 2009; 7:397–414. [PubMed: 19114127]

Nishiguchi S, Kuroki T, Nakatani S, et al. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet. 1995; 346:1051–1055. [PubMed: 7564784]

Nishiguchi S, Shiomi S, Nakatani S, et al. Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis. Lancet. 2001; 357:196–197. [PubMed: 11213099]

Ouyang, G., Pan, G., Li, Q., Li, S., Liu, T., Yi, X., & Liu, Z. (2024). Global burden of acute hepatitis E between 1990 and 2019 and projections until 2030. *Liver International*, *44*(6), 1329-1342.

Palumbo E. Hepatitis B genotypes and response to antiviral therapy: a review. Am J Ther. 2007; 14:306–9. [PubMed: 17515708]

Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1195–206. [PubMed: 21449783]

Recommendations of the Immunization Practices Advisory Committee [ACIP]. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. MMWR Recomm Rep. 1991; 40[RR-13]:1–25.

Resti M, Azzari C, Mannelli F, et al. Mother-to-child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. BMJ. 1998; 317:437–41. [PubMed: 9703524]

Resti M, Bortolotti F, Vajro P, et al. Guidelines for the screening and follow-up of infants born to anti-HCV positive mothers. DigLiver Dis. 2003; 35:453–7. [PubMed: 12870728]

Resti M, Jara P, Hierro L, et al. Clinical features and progression of perinatally acquired hepatitis C virus infection. J Med Virol. 2003; 70:373–7. [PubMed: 12766999]

Ruiz-Extremera A, Salmeron J, Torres C, et al. Follow-up of transmission of hepatitis C to babies of human immunodeficiency virus negative women: the role of breastfeeding in transmission. Pediatr Infect Dis J. 2000; 19:511–16. [PubMed: 10877164]

Schwarz KB, Gonzalez-Peralta RP, Murray KF, et al. Peds-C Clinical Research Network. The combination of ribavirin and peginterferon is superior to peginterferon and placebo for children and adolescents with chronic hepatitis C. Gastroenterology. 2011; 140:450–458. e1. [PubMed: 21036173]

Schwarz KB, Mohan P, Narkewicz MR, et al. Safety, efficacy and pharmacokinetics of peginterferon _2a [40 kd] in children with chronic hepatitis C. J Pediatr Gastroenterol Nutr. 2006; 43:499–505. [PubMed: 17033526]

Shepard, TH. Catalog of teratogenic agents pp 1309. 9. Baltimore, MD: Johns Hopkins University Press; 1998. p. 1309

Sokal EM, Clonjeevaram HS, Roberts EA, et al. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. Gastroenterology. 1998; 114:988–95. [PubMed: 9558288]

Thilagavathi, R., Begum, S. S., Varatharaj, S. D., Balasubramaniam, A. K., George, J. S., & Selvam, C. (2023). Recent insights into the hepatoprotective potential of medicinal plants and plant-derived compounds. *Phytotherapy Research*, *37*(5), 2102-2118

Voeller, A. S., Johannessen, A., Abebe, Z. Z., Adugna, W., Gamkrelidze, I., Seyoum, E., ... & Desalegn, H. (2025). The disease and economic burden of HBV and HCV in Ethiopia. *Journal of Viral Hepatitis*, *32*(2), e14053.

Vogt M, Lang T, Frosner G, et al. Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. N Engl J Med. 1999; 341:866–70. [PubMed: 10498458]

Wang G, Zhang L, Bonkovsky HL. Chinese medicine for treatment of chronic hepatitis B.

Chin J Integr Med. 2012; 18:253–5. [PubMed: 22457135]

Wang J, Zhu Q, Zhang X. Effect of delivery mode on maternal–infant transmission of hepatitis B virus by immunoprophylaxis. Chin Med J. 2002; 115:1510–2. [PubMed: 12490098]

Wen WH, Chang MH, Hsu HY, Ni YH, Chen HL. The development of hepatocellular carcinoma among prospectively followed children with chronic hepatitis B virus infection. J Pediatr. 2004; 144[3]:397. [PubMed: 15001956]

Willner IR, Uhl MD, Howard SC, et al. Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. Ann Intern Med. 1998; 128:111–14. [PubMed: 9441570]

Wirth S, Pieper-Boustani H, Lang T, et al. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. Hepatology. 2005; 41:1013–1018. [PubMed: 15793840]

Wong VC, Ip HM, Reesink HW, et al. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study. Lancet. 1984; 1:1–6. [PubMed: 6140340]

Wörle H, Maass E, Köhler B, Treuner J. Interferon alpha-2a therapy in haemangiomas of infancy: spastic diplegia as a severe complication. Eur J Pediatr. 1999; 158:344. [PubMed: 10206141]

Yeung LT, To T, King SM, et al. Spontaneous clearance of childhood hepatitis C virus infection. J Viral Hepatol. 2007; 14:797–805.

Zeng H, Cai H, Wang Y, Shen Y. Growth and development of children prenatally exposed to telbivudine administered for the treatment of chronic hepatitis B in their mothers. Int J Infect Dis. 2015; 33:97–10. [PubMed: 25449229]

Zhang L, Wang G, Hou W, Li P, Dulin A, Bonkovsky HL. Contemporary clinical research of traditional Chinese medicines for chronic hepatitis B in China: an analytical review. Hepatology. 2010 Feb; 51[2]:690–8. [PubMed: 20101751]

Zhou, D., Zhang, C., Zhang, L., Jia, J., Fu, J., & Cao, Z. (2025). A research protocol for a prospective, multicenter, cohort study on interferon therapy for chronic hepatitis B combined with metabolism-associated fatty liver disease to achieve clinical cure. Frontiers in Public Health, 13, 1546182.