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Review Article

Review Article

Gaps and disparities in the treatment of chronic hepatitis B infection in the USA

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Abstract

Chronic hepatitis B (CHB) infection affects nearly 300 million individuals worldwide and is a leading cause of hepatocellular carcinoma and liver-related mortality. However, major gaps in the CHB cascade of care persist, with the majority of individuals with CHB not diagnosed and not linked to care and treatment. Even among individuals with known CHB, existing studies report on major gaps and disparities in timely linkage to care and timely access to CHB therapies. While the momentum to expand and simplify CHB treatment guidelines is promising, access to treatment still relies on individuals being effectively engaged in clinical care and liver disease monitoring. The contributing factors to the observed gaps and disparities in the CHB cascade of care are complex and multifactorial, and there is no one-size-fits-all solution than can be easily applied across all global regions. However, any serious approach towards addressing the existing gaps in the CHB cascade of care to improve patient outcomes requires a concerted investment from healthcare institutions, governments, policymakers, and industry partners to provide the necessary resources to be able to achieve this goal. Anything less than a comprehensive and collaborative approach that engages all stakeholders to invest effort and resources into tackling the global epidemic of CHB will continue to fall short in making progress towards global viral hepatitis elimination goals.

Keywords: hepatitis B; antiviral; disparities; cascade of care

Introduction

Hepatitis B virus (HBV) infection remains a leading cause of liver-related morbidity and mortality globally and is a leading cause of hepatocellular carcinoma (HCC) worldwide [1, 2]. HBV contributes to significant clinical and healthcare burden, with recent data estimating that nearly 300 million adults are chronically infected with HBV [3, 4]. Despite the significant healthcare burden attributed to chronic hepatitis B (CHB) infection, major gaps and disparities in the CHB cascade of care persist, which contribute to delays in diagnosis and gaps in timely access to CHB antiviral therapies. For example, data from the Polaris Observatory Collaborators estimated that CHB has a global prevalence of 258 million individuals [1, 2]. However, it is particularly alarming that only 36 million of these individuals with CHB have been diagnosed and, furthermore, it is estimated that only 6.8 million individuals with CHB have been treated [1].

In the USA, the most recent data estimate the CHB prevalence to be up to 2.5 million individuals affected [5, 6]. However, similar gaps in the CHB cascade of care have also been reported among US populations. One study by Ye *et al.* [7] utilized data from the Optum Clinformatics database, which is an administrative health-claims database of US adults with commercial or Medicare Advantage insurance coverage. The authors observed that, among CHB patients who were determined to be treatment-eligible based on guidelines, only 60.4% had received antiviral therapy. Unfortunately, these gaps and disparities have been reported across several studies and involve disparities in screening, diagnosis, and linkage to care for CHB patients, ultimately leading to disparities in CHB-related patient outcomes [7–15]. In this review, we highlight the existing data on gaps and disparities in the CHB cascade of care with a focus on current challenges in timely access to CHB therapies.

Chronic hepatitis B cascade of care

The first and perhaps most important step in the CHB cascade of care is to ensure adequate HBV testing and diagnosis (Figure 1). As previously mentioned, the Polaris Observatory Collaborators performed a modeling study to evaluate the prevalence, diagnosis, treatment, and prevention measures for CHB in 2022 [1]. The investigators utilized a dynamic Markov-based model that incorporated data from 170 countries and estimated a global prevalence of CHB of 3.2% (95% confidence interval (CI) 2.7–4.0), which corresponded to 257.5 million individuals (95% CI 216.6–316.4). However, among this burden of CHB, the investigators estimated that only 36.0 million were diagnosed, representing <15% of the total population with CHB. In the USA, Ogawa *et al.* [16] utilized data from the Truven Health Marketscan database, which represents nearly 200 million privately insured adults. The authors

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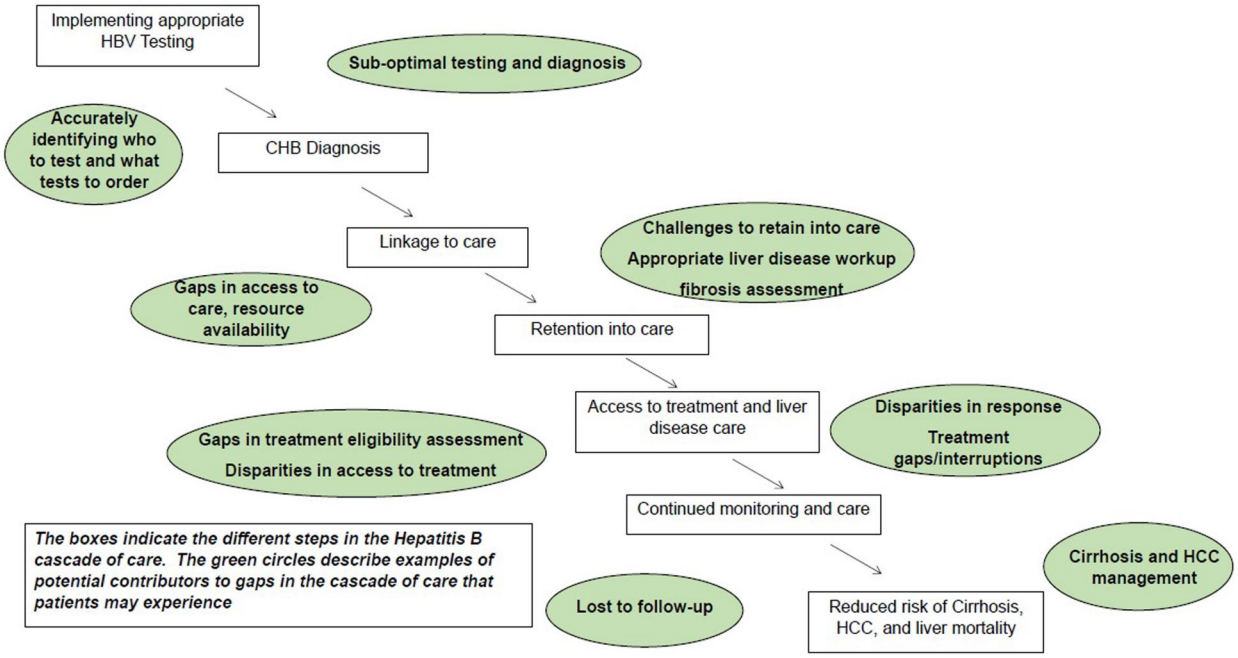

Figure 1. The chronic hepatitis B cascade of care.

identified 511,029 individuals with CHB infection, but estimated that only 18.6% of these individuals were diagnosed with CHB based on a review of the ICD-9/10 insurance claims diagnosis coding. The major gaps in timely diagnosis are reflective of the multifactorial barriers in timely HBV testing, including lack of awareness on both the patient and provider sides, potential patient stigma contributing to barriers in care, confusion over what diagnostic testing to order and how to interpret test results, as well as costs associated with HBV testing, especially in underinsured individuals and among low-resourced settings [7, 11, 14, 15, 17–23].

One potentially modifiable factor in addressing these challenges is to improve the education and awareness of CHB. Zhou *et al.* [15] evaluated data in the USA by using the National Health and Nutrition Examination Survey to evaluate factors associated with awareness of HBV or hepatitis C virus (HCV). The study included a total of 14,745 participants, among whom 68 had HBV infection and 211 had HCV infection. Among individuals with HBV, only 32% reported being aware of their infection status and, among individuals with HCV, only 49% reported being aware of their infection status. The authors identified several factors associated with being aware of their viral hepatitis infection status, including country of birth, level of education completed, race/ethnicity, household income level, marital status, and whether the individuals reported active injection drug use. These data illustrate that both socio-demographic and socio-economic factors are likely at play, contributing to gaps in awareness and accurate perception of the dangers of CHB infection. Similarly, Wong *et al.* [24] evaluated patients with CHB at a large single-center safety-net hospital in the USA to evaluate gaps and disparities in the awareness of CHB. Among individuals who had received prior testing for HBV, only 18.4% were aware of their results. However, lack of awareness or lack of knowledge regarding HBV is a modifiable factor that can be addressed through targeted interventions and outreach programs. For example, Wong *et al.* [23] prospectively evaluated the impact of a formal patient educational intervention on improving HBV knowledge as well as HBV monitoring and treatment in a single-center urban safety-net health system in the USA. A total of 151 consecutive adults with CHB were identified. Participants completed a questionnaire to assess their ability to identify facts regarding HBV transmission and to identify patient characteristics and risk factors that are associated with a higher risk of HBV, as well as the importance of HBV treatment in reducing the risk of disease progression as well as HCC, before and immediately following the completion of an in-person formal patient educational intervention. HBV knowledge increased by 25% following the educational intervention, and patients had significant improvements in appropriate HBV clinic follow-up, appropriate HBV laboratory monitoring, appropriate HCC surveillance, and initiation of HBV treatments [25].

While efforts to improve the effective implementation of HBV screening programs are important, it is equally important to ensure that individuals with diagnosed CHB are successfully linked to care and treatment. Persisting delays along subsequent steps in the HBV care cascade (e.g. linkage to care, assessment of treatment eligibility, initiation of antiviral therapy among treatment-eligible CHB patients) create major gaps and delays in CHB care, allowing continued disease progression [20, 26–28]. Improving linkage to care and timely antiviral therapy for CHB is critical given the robust data demonstrating the effectiveness of antiviral therapy in reducing the long-term risks of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality [29–33].

The HBV cascade of care is complex (Figure 1) and there is a need for targeted interventions to more effectively link CHB patients to care [20, 26–28]. The importance of timely linkage to care and treatment is reflected by robust data showing the effectiveness of existing antiviral therapies at suppressing HBV DNA and lowering the long-term risks of cirrhosis, cirrhosis-related complications, HCC, and liver-related mortality [29–35]. Despite the importance of timely diagnosis and treatment, significant delays in CHB linkage to care and treatment have been observed, especially among vulnerable populations, including ethnic minorities and socio-economically disadvantaged groups. For example, among a single-center safety-net cohort of 454 CHB patients in the USA (72% Asian, 21% African American), the study observed that only 63% of patients with CHB were successfully

linked to an HBV provider [20]. This is a critical gap in the CHB cascade, as not being linked to providers who have experience and expertise with CHB monitoring in treatment may lead to significant delays in timely assessment for treatment eligibility and the initiation of appropriate antiviral therapies. Furthermore, among CHB patients who were successfully linked to care in the aforementioned study, only 70% were retained in that care (defined as two additional visits beyond the initial linkage to care) [20]. This emphasizes not only the importance of ensuring successful linkage to care initially after the diagnosis of CHB, but also the need for long-term engagement in that care so that appropriate monitoring and treatment can be implemented. The clinical impact of delays in diagnosis and linkage to care can be observed in a subsequent study among this same cohort, which demonstrated that 27% of patients with CHB had already developed cirrhosis at the time of diagnosis [36]. Another study using data from the US REACH cohort evaluated 53,896 ethnic minority adults to evaluate disparities in healthcare delivery among minority communities. Among this cohort (40% African Americans, 30% Asian), only 39.2% of eligible patients received appropriate HBV screening. Similarly, concerning, among adults who were diagnosed with CHB, only 33% were successfully linked to an HBV provider [37]. These studies continue to highlight existing gaps in the early steps of the CHB cascade of care, from screening to linkage to care. Better identification of the contributors to these gaps is critical so that further research and novel targeted interventions can be implemented to improve the cascade of care, given that these existing gaps ultimately lead to downstream delays in timely access to CHB treatment, contributing to worse patient outcomes.

Furthermore, it is important to identify and empower stakeholders to lead efforts to bridge these gaps in the CHB cascade of care. For example, the evolution of health policies (e.g. screening and vaccination recommendations) is important to not only guide clinicians, but also provide an important framework that medical societies as well as payors can use to further improve patient care. Health systems and payors need to work together and collaborate to develop effective systems to track CHB patients along the cascade of care, develop quality metrics, and incorporate innovative features into electronic health records to improve the consistency of care delivery. Pharmaceutical industry partners are important stakeholders as well and, in addition to ensuring affordability and access to CHB therapies, these partners can help to fund or support research and quality improve projects to further mitigate the gaps and disparities in the CHB cascade of care.

Disparities in CHB treatment

The downstream effects of delays in diagnosis and linkage to care are that they further contribute to delays in the timely assessment of CHB treatment eligibility and the start of antiviral therapy. As previously mentioned, the Polaris Observatory Collaborators evaluated gaps in the cascade of CHB care, including treatment, on a global scale [1]. In their modeling study, among the estimated 83.3 million adults with CHB who were treatment-eligible, the investigators estimated that only 6.8 million received antiviral therapy. This major gap in the timely treatment of CHB is a major concern given that untreated CHB allows continued liver disease progression to cirrhosis and HCC. In the USA, similar gaps and disparities in CHB have been observed. In a recent study of 5,157 patients with CHB patients across four US safety-net health systems from 2010 to 2018, the investigators observed that only 37.3% of treatment-eligible patients received antiviral therapy [38]. Data from Ogawa *et al.* [16] utilizing the US Truven Marketscan insurance claims dataset observed even more concerning findings: among adults with CHB-related cirrhosis, only 34.8% were on CHB antiviral therapies. These data are aligned with those of another recent study that evaluated treatment gaps among US Veterans with CHB-related cirrhosis. Among a national cohort of >12,000 Veterans with CHB, the investigators evaluated gaps and disparities in treatment specifically for those who had already developed cirrhosis [10]. Among the 2,550 Veterans with CHB cirrhosis, 52.0% received antiviral therapy. Important disparities were also observed. For example, when compared with Asians with CHB cirrhosis, the investigators observed significantly lower rates of CHB treatment among African Americans (47% vs 81%, $P < 0.01$), non-Hispanic whites (51% vs 81%, $P < 0.01$), and Hispanics (64% vs 81%, $P = 0.02$) [10]. A more recent study from the Hepatitis B Research Network evaluated 1,550 patients with CHB, among whom 12% were African American, 75% were Asian, and 10% were white [12]. During 5,727 person-years of follow-up, 504 patients initiated antiviral therapy. The authors observed that African Americans were less likely to meet treatment-eligibility criteria than other race groups but, among those who did meet treatment eligibility, no significant differences in the cumulative probability of CHB treatment were observed [12].

In addition to race/ethnicity-specific disparities in CHB treatment, major gaps and disparities in CHB care have also been observed between men and women. For example, Tang *et al.* [20] observed that, among a single-center safety-net health system of patients with CHB, although men and women had similar rates of successful linkage to care after CHB diagnosis, continued retention in that CHB care and monitoring was significantly lower in women compared with men (60.7% vs 76.5%, $P < 0.001$). A recent multinational study of 12,566 patients with CHB across nine countries also evaluated gender-specific disparities in CHB treatment. Among the patients who were eligible for CHB treatment based on the American Association for the Study of Liver Diseases (AASLD) criteria, 83.3% were initiated on antiviral therapy, but women were 50% less likely to be treated compared with men [9]. Another recent study from Wong *et al.* [8] evaluated 3,749 patients with treatment-naive CHB across three US safety-net health systems. Overall, the investigators observed that 30.0% were treatment-eligible based on AASLD criteria, but only 31.0% of those who were eligible received antiviral therapy. Significant disparities in treatment were observed, especially along gender lines. Among treatment-eligible patients, men were significantly more likely to receive timely antiviral therapy compared with women (33.5% vs 26.6%, adjusted hazard ratio 1.21, $P < 0.01$). These data and others continue to highlight both race/ethnicity and gender-specific disparities in CHB treatment, even among the subset of patients who meet eligibility criteria [7–9, 11, 12, 39]. While the exact contributors to these persistent disparities are not clear, more research is needed to raise awareness of these persisting disparities and to better understand and develop novel interventions to mitigate treatment disparities among adults with CHB.

Although the factors contributing to existing gaps and disparities in CHB are multifactorial, one potential factor is the complexity and heterogeneity of existing CHB treatment guidelines that may create confusion and unintended barriers to the effective implementation of CHB treatment. As previously noted, the beneficial effect of CHB antiviral therapies in effectively suppressing HBV DNA replication, leading to reduced long-term risks

of disease progression and HCC, is robust [33, 34, 40]. Despite these robust data, guidelines for CHB treatment are at times contradictory, and recommendations regarding treatment eligibility are heterogenous and complex, incorporating various factors, such as an individual's age, country of origin, family history, comorbidities, liver disease severity, HBV e antigen status, alanine aminotransferase levels, and HBV DNA levels [41–43]. The complexity of existing CHB guidelines are also continuing to evolve and providers who are caring for CHB patients may not be up to date with the most recent recommendations or may feel unclear about the interpretation of existing guidelines to determine treatment eligibility. However, there is building momentum to simplify and expand CHB treatment criteria [4, 44–46], fueled by the growing body of evidence that antiviral therapy may be beneficial even among individuals who do not meet the strict eligibility criteria. For example, Huang *et al.* [47] performed a retrospective multicenter, multinational cohort study of 3,366 adults with CHB. Among this cohort, the investigators identified 1,303 individuals with CHB who were in the indeterminate phase and hence not eligible for antiviral therapy based on existing guidelines. Over a 10-year follow-up, 52.7% of patients with CHB remained in the indeterminate phase whereas 21.7% of patients transitioned into the immune active phase. Compared with those who remained in the inactive phase, individuals who remained in the indeterminate phase had a significantly higher long-term risk of developing HCC (4.6% vs 0.5%, aHR 14.1, $P = 0.03$). This risk was even higher among individuals who were aged ≥45 years (aHR 18.4, $P = 0.005$). Similarly, Sinn *et al.* [48] performed a retrospective multicenter study of 3,624 adults with untreated CHB. During a median follow-up of 4.6 years, 161 patients developed HCC. Among the patients who developed HCC, 64.0%, 46.0%, and 33.5% did not meet CHB treatment-eligibility criteria according to guidelines by the Asian Pacific Association for the Study of the Liver, the AASLD, and the European Association for the Study of the Liver (EASL). As previously noted, given the increasing evidence showing potential clinical benefit in the treatment of patients who are outside the traditional eligibility criteria, many societies and organizations (e.g. World Health Organization, Chinese Medical Society) either have or are in the process of updating CHB treatment recommendations that will likely lead to more broad acceptance of treating patients with CHB with any detectable HBV DNA [4, 46]. However, while the enthusiasm and evidence in support of expanding antiviral treatment-eligibility criteria are building, it is important to recognize that the expansion of treatment criteria does not directly address the existing gaps in the CHB cascade of care. It has been reported that, even with existing stricter treatment criteria, major gaps and disparities in timely access to CHB treatment are observed. With the gradual expansion of treatment criteria, one must ask whether there are adequate resources to allow us to meet the challenge of the potential increasing cohort of treatment-eligible CHB patients. While the movement and advocacy of expanding antiviral treatment criteria are building, there must be renewed energy and prioritization to address existing major gaps in the CHB cascade, including ensuring the effective implementation of screening and vaccination, as well as linkage to care and treatment. Success in mitigating these gaps in parallel with the expansion of the treatment criteria will require the investment of resources and workforce to be able to meet this challenge.

Conclusions

The existing gaps in the CHB cascade of care that have been reported across studies are a major concern and concerted efforts are needed to improve CHB care. First, there is a need to improve the effectiveness of HBV screening. This requires education to raise awareness amongst providers, especially primary-care providers, who often serve as the continuity of care for patients. In parallel, increased efforts must be made to educate and raise awareness among patient populations, especially individuals who are considered to be in high-risk groups for CHB infection. In addition to education, affordable and highly accurate HBV assays are needed as well as testing modalities that offer rapid turnaround and can be conducted in nontraditional settings (e.g. point-of-care testing). While effective implementation of HBV testing and diagnosis is perhaps the most important first step in the CHB cascade of care, ensuring that diagnosed patients are successfully linked to care is equally important. As noted above, globally, the vast majority of CHB patients have not been diagnosed and thus are not linked to care for continued monitoring. The gaps in linkage to care in monitoring are barriers to the timely assessment of CHB treatment. Even if CHB treatment guidelines were expanded or simplified, effectively bridging the existing gaps in diagnosed CHB patients to linkage to care is critical in accessing antiviral therapies. Finally, major gaps and disparities in CHB treatment have been observed. The contributors to these gaps are multifactorial and vary by population, region, and availability of healthcare resources. The movement to simplify and expand existing CHB treatment guidelines is promising and will remove some barriers to timely access to CHB treatment. However, the solution to address treatment gaps in CHB is complex and requires not only efforts on the parts of patients and providers, but also a concerted investment from healthcare institutions, governments, policymakers, and our industry partners to provide the necessary resources to seriously tackle this epidemic. Without a true collaborative approach and investment in effort and resources, the goal of viral hepatitis elimination will continue to remain beyond our reach.

Authors' Contributions

Study concept and design: R.J.W. Drafting of the manuscript: R.J.W. Critical revision of the manuscript for important intellectual content: R.J.W. R.J.W. approved the final version of this manuscript.

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Conflicts of Interest

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