International HBV Treatment Guideline Evaluation

Subjects: Pathology | Virology

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There are five international hepatitis B virus (HBV) treatment guidelines: AASLD, APASL, EASL, NICE, and WHO. All guidelines recommend treatment based on levels of HBV DNA, alanine aminotransferase (ALT), age, and liver fibrosis. Among five guidelines, only the WHO guideline recommends the aspartate aminotransferase-to-platelet (APRI) to evaluate liver fibrosis as an alternative to elastography.

Keywords: chronic human hepatitis ; DNA viruses ; elastography ; Hepadnaviridiae ; viral diseases

1. Introduction

Hepatitis B Virus (HBV) Infection

Hepatitis B virus (HBV) infects the liver and can cause chronic hepatitis with necrosis and inflammation, which sometimes results in liver failure, cirrhosis and hepatocellular carcinoma (HCC) [1]. Chronic HBV infection is defined as persistent infection with detectable hepatitis B surface antigen (HBsAg) for longer than six months in the presence or absence of evidence showing active viral replication, hepatocellular injury, or inflammation [2]. In the world, two billion people are infected with HBV, and 260 million people are chronic carriers [3][4]. The World Health Organization (WHO) estimated 887,000 deaths from hepatitis B, mainly from cirrhosis and HCC [5].

HBV Diagnosis and Monitoring

Antigen and antibody detection: A laboratory diagnosis of HBV infection depends on the detection of either the viral antigens [HBsAg and hepatitis B envelope antigen (HBeAg)], or anti-HBV antibodies [anti-HBsAg (anti-HBs), anti-hepatitis B core antigen (anti-HBc), and anti-HBeAg (anti-HBe) antibodies], in blood samples [2]. HBsAg detection is used for screening of HBV infection in the clinical setting. The presence of HBsAg or HBeAg in the blood indicates HBV infection and active HBV replication. The presence of anti-HBe antibody indicates spontaneous improvement with a decline in the viral replication. The anti-HBs antibody is recognized as the marker of immunity after vaccination. The presence of anti-HBs and anti-HBc antibodies indicates past infection [6][7].

DNA-PCR: The presence of HBV-DNA in serum or plasma indicates active HBV infection. The HBV viral loads (HBV DNA concentration) quantified by real-time polymerase chain reaction (PCR) have been used to evaluate disease progression and to help in decision-making for subsequent treatment or monitoring [7].

Assessment of liver: There are invasive and non-invasive methods for the assessment of the liver. For the non-invasive method, liver enzymes and platelet counts can be used. Liver enzymes include alanine aminotransferase (ALT) and aspartate aminotransferase (AST). AST-to-platelet ratio index (APRI) is used as an alternative non-invasive method to assess cirrhosis in resource-limited settings, although liver fibrosis can be detected by biopsy or magnetic resonance elastography [2].

2. Five International HBV Treatment Guidelines

There are five international treatment guidelines for HBsAg-positive patients: 1. American Association for the Study of Liver Diseases (AASLD), 2. Asian Pacific Association for the Study of the Liver (APASL), 3. European Association for the Study of the Liver (EASL), 4. National Institute for Health and Care Excellence (NICE), and 5. World Health Organization (WHO). The guidelines are based on HBV DNA level, ALT level, age, HBeAg status, and liver fibrosis (**Table 1**) [8][9][10][11][12], and divide the HBV patients into three categories: no treatment, monitoring, and treatment.

American Association for the Study of Liver Diseases (AASLD)

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The decision of whether to initiate HBV treatment is based on viral loads, ALT levels, and severity of liver disease, as well as age, health status, family history, and hepatic manifestations [4]. Patients with chronic HBV infection without cirrhosis is treated if they have persistently increased ALT levels (> 2 x ULN) for at least 1 month and HBV DNA levels of more than 20,000 IU/mL (with positive HBeAg) or HBV DNA levels of more than 2000 IU/mL (with negative HBeAg) [4]. This guideline also considered for treatment of patients with compensated cirrhosis and the HBV DNA levels of less than 2000 IU/mL, and even if their levels of ALT are normal. Liver cirrhosis is assessed by a non-invasive method by using Fibroscan or APRI, although liver biopsy is a recommended method. Biopsy is mandatory if non-invasive tests suggest evidence of significant fibrosis, age >35 years, ALT is persistently elevated, or there is a family history of HCC or cirrhosis.

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The decision of whether to initiate HBV treatment is based on the combinations of three criteria: the HBV DNA levels, ALT levels, and severity of liver diseases as determined by biopsy or elastography. This guideline recommends for no treatment if a person with HBV DNA levels of less than 2000 IU/mL and normal ALT levels. Patients under 30 years of age with high HBV DNA levels and no evidence of liver disease are not immediately treated but should be kept on follow-up [14]. The EASL recommends treatment for patients with HBV DNA levels of more than 20,000 IU/mL and abnormal ALT levels (> 2 x ULN) [14]. It also suggests treatment for the patients if their HBV DNA levels exceed 2000 IU/mL, ALT levels are elevated, and active necrosis/inflammation in the liver is observed.

National Institute for Health and Care Excellence (NICE, UK)

The decision of whether to initiate HBV treatment is based on viral loads, ALT levels, age and liver cirrhosis. This guideline recommends for no treatment if a person with HBV DNA levels of less than 2000 IU/mL and normal ALT levels in all ages. In the patients younger than 30 years of age with HBV DNA levels of more than 2000 IU/mL and abnormal ALT levels in two consecutive tests at 3-month intervals, treatment is initiated only if there is evidence of severe hepatitis or fibrosis. The treatment should be initiated for the patients aged 30 years or older with HBV DNA levels of more than 2000 IU/mL and abnormal ALT levels (≥30 IU/L in males and ≥19 IU/L in females) in two consecutive tests at 3-month intervals. The NICE recommends treatment for patients with HBV DNA levels of more than 20,000 IU/mL and abnormal ALT levels in two consecutive tests at 3-month intervals; treatment can be initiated regardless of the patient's age or the extent of liver disease [15].

World Health Organization (WHO)

The decision of whether to initiate HBV treatment is based on viral loads, ALT levels, age and liver cirrhosis. This guideline recommends for no treatment of a person with HBV DNA levels of less than 2000 IU/mL and persistently normal ALT levels without clinical evidence of cirrhosis [2]. Continuous monitoring is required for patients under 30 years old with HBV DNA levels of more than 20,000 IU/mL and persistently normal ALT levels, as well as for those with HBV DNA levels of 2000–20,000 IU/mL. The WHO recommends treatment for all patients with cirrhosis as well as the patients with HBV DNA levels of more than 20,000 IU/mL and persistently abnormal ALT levels without cirrhosis, particularly those older than 30 years of age [2]. Although elastography may be preferred for developed countries, the WHO guideline recommends the APRI to assess the presence of cirrhosis (APRI > 2) in resource-limited settings, along with viral loads, ALT levels to determine the treatment of HBV infection.

3. Anti-viral Therapy of HBV Infection

All five international guidelines also described the antiviral therapy of HBV infection. The main objective of antiviral therapy is to decrease the morbidity and mortality related to chronic HBV infection by delaying the progression of cirrhosis, reducing the incidence of HCC, and improving long-term survival. There are two options for antiviral agents;

either interferon (IFN)-based therapy including peg-IFN, or nucleos(t)ide analogs-based therapy including lamivudine, telbivudine, entecavir, adefovir, tenofovir, and emtricitabine. The WHO recommends monitoring of ALT, HBsAg, HBeAg, HBV DNA levels, and APRI scores for liver cirrhosis assessment during the treatment at least once a year.

4. Conclusion

All guidelines recommend treatment based on levels of HBV DNA, ALT, age and liver fibrosis. Among five guidelines, only the WHO guideline recommends the APRI to evaluate liver fibrosis as an alternative to elastography [16].

Table 1: Five International HBV Treatment Guidelines

Guidelines	HBsAg	Viral load (IU/mL)	ALT	Age (yr)	HbeAg	Liver fibrosis
1. AASLD	Positive	>20,000	>2 x ULN	>40	Positive	Elastography
2. APASL	Positive	>20,000	>2 x ULN	>35	Positive	Elastography
3. EASL	Positive	>20,000	>2 x ULN	>30	NA	Elastography
4. NICE	Positive	>20,000	Abnormal	All	NA	Elastography
5. WHO	Positive	>20,000	Abnormal	> 30	NA	Elastography or APRI (>2)

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; APRI, aspartate aminotransferase-to-platelet ratio index; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B envelope antigen; HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable; NICE, National Institute for Health and Care Excellence; ULN, upper limit of normal; and WHO, World Health Organization.