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Review Article

Management of Hepatitis B: A Review of the Literature

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Abstract

Hepatitis B virus (HBV) remains a global health problem and for this reason, prevention programs have been implementing and new drug have been developed. Initially, we should evaluate the seriousness and duration of hepatitis B and then we should select the appropriate treatment. The current treatment of chronic hepatitis B is with pharmaceutical agents. Drugs divided into two categories: (peg)-interferon and nucleos(t)ide analogues. On the one hand interferon offers finite treatment but it is correlated with serious side effects. On the other side nucleoside analogues have weak side effects, but long-term treatment is required. From nucleos(t)ide analogues, tenofovir and entecavir are usually used as first line treatment due to potently inhibition of HBV replication and high barrier resistance. End points of treatment depend on case, if patient is HBeAg negative or positive and the degree of liver injury. Patients should be monitored during treatment for the control of viral response and after treatment due to risk of viral relapse. Monitoring includes biochemical and virological control. Because patients with hepatitis B risk developing hepatocellular carcinoma, they should be screened periodical with ultrasound and a-fetoprotein.

Keywords: *Treatment of Hepatitis B; Prevention; Extrahepatic Manifestations; Natural History*

Abbreviations

AASLD: American Association for the Study of Liver Diseases; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; EASL: European Association for the Study of the Liver; GFR: Glomerular Filtration Rate; PAN: Polyarteritis Nodosa; TAF: Tenofovir Alafenamide; TDF: Tenofovir Disoproxil Fumarate; US: Ultrasound

Introduction

Hepatitis B is a worldwide health problem, especially in developing areas. It is estimated that one third of the population has serological evidence of past or present infection with HBV, including 400 million who have chronic hepatitis B [1,2]. The prevalence of HBV infection varies notably around the world. So, in the highest endemic regions, such as East Asia, up to 8.6% of the population are chronic HBV carriers, while in Western Europe and North America the incidence is below 2% [3]. The range of natural history and clinical manifestations is various and vacillating from inactive carrier state to progressive active hepatitis B, which may lead to hepatocellular carcinoma and/or cirrhosis [4].

Clinical presentation and natural history

The spectrum of clinical manifestation of hepatitis B varies with the individual and the disease phase. During the acute HBV infection, clinical symptoms range from malaise, nausea and arthralgias to fulminant hepatitis with jaundice, encephalopathy and coagulopathy. During the chronic HBV infection, manifestations range from asymptomatic carrier to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC). Hepatitis B virus can be transmitted parenterally (blood, sperm, vaginal fluids) and perinatal. The incubation period after HBV infection ranges from 60 to 150 days. Complete recovery and development of protective immunity occurs more than 95% of

patients infected as adults or adolescent. However, the recovery rate drops to 30% for young children and is only 5% for newborns that were infected during the birth from their mother [5]. The chronic hepatitis B infection can be divided into four phases: 1."immune tolerant'' phase, 2. HBeAg positive immune-active phase, 3. inactive chronic hepatitis B phase, 4.HBeAg-negative immune reactivation phase (Figure 1) [6].

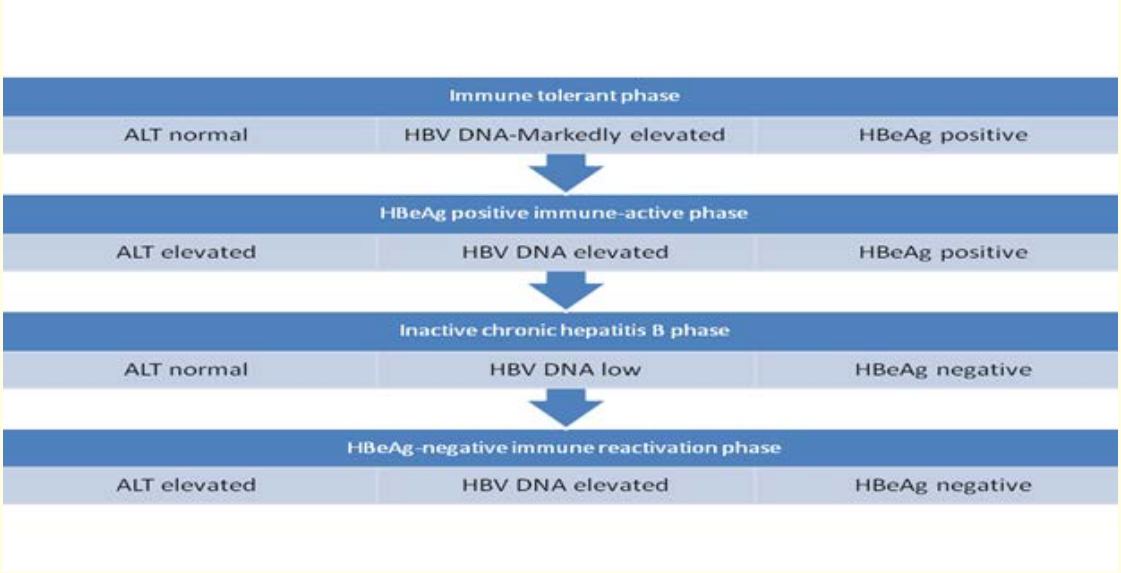

Figure 1: *Phases of chronic hepatitis B infection.*

Hepatitis B Virus

HBV is a partially double-stranded DNA virus that belongs to Hepadnaviridae family and is classified into eight genotypes (A-H) and four main serotypes (adr, adw, ayr, ayw) based on antigenic epitopes, that present on its envelope proteins [7]. Genotyping tests are used for HBeAg positive patients who may be treated with interferon, because genotypes A and B are associated with higher rates of seroconversion, after therapy Pegylated-interferon [8,9]. On the other hand, genotype C is associated with an increased risk for HCC development [10]. Also, it seems that genotypes influence the progress of disease [11].

Diagnosis

People, who have a high risk for HBV infection, should be tested (Table 1) and then if there is HBV infection, it is important to distinguish between acute and chronic. Patients, who are infected with acute hepatitis B test positive for: HBsAg and IgM-HBc or only IgM-HBc (window phase) for less than 6 months. Persons, who are positive for HBsAg for more than 6 months, are chronically infected with HBV. The detection of Hepatitis B e antigen (HBeAg) is associated strongly with active viral replication and high infectivity. The persons who are seronegative for HBsAg, HBsAb and anti-HBc should be vaccinated.

Persons who should be tested
Persons born in high or immediate endemic areas
Persons with chronically elevated aminotransferases
Person needing immunosuppressive therapy or chemotherapy
Men who have sex with men
Persons with multiple sexual partners or history of sexual transmitted disease
Inmates of correctional facilities
Persons who have ever use injecting drugs
Dialysis patient
Persons who are exposed to blood and body fluids on the job
HIV or HCV-infected individuals
Pregnant women
Family members, household members and sexual contacts of HBV infected persons.

Table 1: *People, who should be tested for HBV according to American Association for the Study of Liver Diseases (AASLD) practice guidelines of Hepatitis B Virus.*

Management of HBV infection

Acute HBV infection

Clinical symptoms of acute HBV infection can include malaise, nausea, vomiting, arthralgias and rash. In the majority of patients with acute HBV, the infection resolves spontaneously and the treatment is only supportive. However, approximately 1% of patients with acute HBV develop acute liver failure and can be recognized by liver synthetic dysfunction, encephalopathy and renal impairment. Severe hepatitis performs two of the following three criteria: 1. hepatic encephalopathy, 2. serum bilirubin > 10 mgr/dL, 3. INR > 1.6. In this setting, the use of an oral anti-HBV agent may be useful [12,13]. Lamivudine is preferred [14] contrary to interferon, which is contraindicated. The duration of treatment is not defined. As a general rule, treatment should be continued until HBsAg seroconversion [15].

Chronic HBV infection

The clinical image of patients with chronic HBV infection is varied and ranges from asymptomatic periods to jaundice and signs of liver failure. The initial assessment of chronic hepatitis B should include:

1. **Estimation of the liver injury and function**: that includes measurement biochemical markers such as AST, ALT, alkaline phosphatase, LDH, γ-GT, total and direct bilirubin, INR, serum albumin and globulins, blood counts.
2. **Specific HBV testing: HBsAg, HBeAg, anti-HBeAg and serum HBV DNA levels**: Measurement of HBV DNA is essential for the diagnosis, indication to therapy and follow-up of patients. Usually, the HBV DNA test is performed using PCR.
3. **Exclusion of other causes of liver disease** such as, steatohepatitis, alcoholic hepatitis (history consumption of alcohol, AST/ALT>2), autoimmune hepatitis (control auto-antibodies ASMA, ANCA, anti-LKM, anti-SLA) hemochromatosis and search for co-infection with hepatitis A virus (anti-HAV), hepatitis C virus (anti-HCV) and/or HIV. Patients, who are anti-HAV negative, should be vaccinated. US should be confirmed to exclude the existence of HCC.
4. **Assessment of liver necroinflammation and fibrosis**: The assessment usually includes biopsy which is an invasive method, but non-invasive methods have been developed (elastography and serum markers) [16,17].
5. **Assessment of other diseases which can influence treatment decision**: Such as heart failure and renal dysfunction. Also, search for extra hepatic manifestations of HBV infection such as rash, arthritis and polyarteritis nodosa.
6. **Research for hepatitis D virus:** (HDV) co-infection (control anti-HDV). HDV is a RNA virus that is dependent on the present of HBsAg for replication. Two types of HDV infection are possible: coprimary infection and superinfection. It is estimated that 5% of HBV

carriers worldwide be infected with HDV [18]. Co-infection of HDV increases the risk for severe liver injury and eventually development of hepatocellular carcinoma [19,20].

Treatment

Who should be treated

The goal of treatment of chronic hepatitis B is to prevent the progression of liver disease and reduction of the risk of transmission and complications (cirrhosis and hepatocellular carcinoma).

According to guidelines from the European Association for the Study of the Live (EASL), patients with chronic HBV infection should be treated when they fulfill the below qualifications [21]:

- HBV DNA levels > 2000 IU/ml Serum ALT> upper limit of normal (ULN) Biopsy shows moderate/severe necroinflammation or fibrosis
- Patients with HBV DNA > 20,000 IU/ml and ALT > 2xULN should start treatment regardless of the degree of fibrosis
- Patients with ALT > x2 ULN and serum HBV DNA > 20,000 IU/ml indicated for treatment regardless of the degree of fibrosis.
- Patients with HBeAg –positive chronic HBV infection, defined by persistently normal ALT and high HBV-DNA levels should be treated if they are older than 30 years old regardless of the degree of liver histological lesions.
- Patients with compensated cirrhosis and detectable HBV DNA must be considered for treatment even ALT levels are normal.
- Patients with decompensated cirrhosis, with any detectable HBV DNA and regardless of ALT levels require treatment with nucleosides analogue. Interferon is contraindicated.
- Treatment is indicated in HBsAg-positive patients who receive chemotherapy or immunosuppressive (prevention of reactivation).
- Patients with family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled.

Available drugs

Current therapy of chronic HBV infection includes eight drugs. Seven of these agents are nucleos(t)ide analogs (lamivudine, telbivudine, emtricitabine, entecavir, adefovir, tenofovir disoproxil fumarate, tenofovir alafenamide) that inhibit the viral DNA polymerase to suppress HBV replication. The other two are interferon and pegylated-interferon.

Interferon: The major advantages of (PEG)-interferon compare to the other drugs (NAs) are the absence of resistance, its finite duration and higher rates of anti-HBe and anti-HBs seroconversion with 12 months of therapy. Approximately 30% and 40% of patients with HBeAg-positive and HBeAg-negative respectively, have a sustained virological response after treatment with pegylated interferon a-2a [22]. The main disadvantages are side effects and subcutaneous injections. Side effects include flu-like symptoms such as malaise and fatigue, hematological effects (neutropenia, thrombocytopenia and anemia), exacerbations of autoimmune diseases and psychological effects such as depression and psychosis. Furthermore, interferon therapy have correlated with thyroid dysfunction, with both hypothyroidism and hyperthyroidism occurring. So, thyroid hormones should be monitored during therapy [23]. Additional, interferon must not be used in patient with decompensated cirrhosis because of risk to occur bacterial infection and exacerbation of liver disease. Interferon is contraindicated during pregnancy, in patients with severe depression and autoimmune diseases.

The most important pretreatment predictors of response to (PEG) - interferon are high pretreatment ALT levels (> 2 ULN), low HBV DNA and genotypes A and B compare to genotypes C and D. On treatment predictor of HBeAg seroconversion is significant decrease of HBV DNA levels < 20,000 IU/ml in 24 weeks [24]. Also, response is most likely to occur when the reduction of HBV DNA is related with ALT flares [25].

Usually, interferon is used in patients with well compensated liver disease, who desire a short-term therapy and not planning to get pregnant.

The main advantages of nucleos(t)ides analogues treatment are oral administration, potent antiviral effect and good tolerance. On the other hand, indefinite duration and risk of resistance are the most important disadvantages.

Lamivudine is a reverse transcriptase inhibitor and it is an inexpensive drug compared to the other NAs. It is a potent inhibitor of HBV replication and HbeAg seroconversion occurs approximately in 20% of patients at first year [26]. In addition, lamivudine benefits HBeAg negative patients as it is related with high biological and virological response rates [27]. However, lamivudine is associated with a high incidence of resistance and this is the main disadvantage of lamivudine. The rate of resistance is approximately 24% after 1 year of lamivudine therapy and increases to 70% after 5 years. Lamivudine is also used for treatment of HIV but at higher doses. So, lamivudine is only used in persons who require only short-term therapy. For example, patients who undergo chemotherapy.

Adefovir is an inhibitor of reverse transcriptase and DNA polymerase. Adefovir resistance occurs less frequently than lamivudine and the rate of resistance is null at first year of therapy but it is 29% after 5 years of treatment. Adefovir is effective in patients with lamivudine-resistance HBV as well as wild type HBV. Adefovir benefits HBeAg-positive patients as HBeAg seroconversion is approximately 50% after five year of therapy [28]. Furthermore, adefovir is also beneficial in patients with HBeAg negative as it helps histological improvement, normalization of ALT and decrease serum HBV DNA [29]. However, adefovir at high doses (30 mg) is nephrotoxic and this reduces its efficacy because of using lower doses (10 mg). The monitoring of kidney function is necessary [30]. Also, adefovir can cause Fanconi's syndrome and hypophosphatemic osteomalacia [31].

Telbivudine is an inhibitor of HBV replication and it is more expensive than lamivudine. Telbivudine is associated with a high incidence of resistance that is lower compared to lamivudine resistance. The rate of resistance is approximately 5% after 1 year of telbivudine treatment and increases to 11% after 2 years. Telbivudine is more effective than lamivudine in treatment-naïve patients [32]. Additional, it seems that telbivudine plays a renoprotective role [33] and is associated with improvements in glomerular filtration rate (GFR) that are maintained for up to 6 years [34]. So, the drug may be a safe and beneficial therapy in patients with preexisting renal impairment. On the other hand, elevations of creatine kinase are common side effect of therapy with telbivudine, while myopathy and peripheral neuropathy are rare [35,36].

Entecavir is a selective guanosine analogue and it has low rate of drug resistance (1 - 2% after five years treatment) [37]. Entecavir is a significant inhibitor of HBV replication in naïve-patients, as HBeAg seroconversion is 21% after one year and 40% after three year of treatment [38]. Entecavir is less effective in patients with developed lamivudine-resistance. Thus, it is not recommended as first line treatment in these patients as 8% of them, when treated with entecavir, develop entecavir resistance during the first year [39]. Entecavir can be used as first line therapy especially in patients with decompensated cirrhosis due to high barrier resistance, its safety and potent activity. Lactic acidosis has been reported during treatment with entecavir and it seems to be associated with impaired liver function [40].

Tenofovir disoproxil fumarate (TDF) is a reverse transcriptase inhibitor and is molecular similar to adefovir. It is less nephrotoxic than adefovir, so the approved dose is higher. Tenofovir is more effective than adefovir both in HBeAg-positive patients and in HBeAg-negative patients [41]. TDF appears a high barrier to resistance, no cases reported after 5 years of treatment [42]. In cases of resistance to lamivudine, telbivudine and entecavir, TDF should be first-line therapy. TDF is also licensed for HIV infection and can be used in HBV/HIV co-infection. The nephrotoxicity is the major side effect of tenofovir and tubular damage and Fanconi syndrome have been observed [43]. Secondary osteomalacia due to Fanconi's syndrome is very rare [44]. It seems that nephrotoxicity is more frequent in persons with HIV co-infection. Monitoring GFR and phosphate levels are recommended for all patients treated with tenofovir, every 3 months during the first year and every six months thereafter [45].

Tenofovir alafenamide (TAF) is nucleotide reverse transcriptase inhibitor and an oral prodrug of TDF. TAF compared to TDF presents higher cell delivery to the hepatocytes but less systematic exposure. Also, clinical demonstrated TAF was nοτ inferior to achieving viral suppression and has better renal and bone safety compared to TDF [46]. TAF is not required dose adjustments in patients until eGFR is < 15 ml/min who are not receiving haemodialysis [47].

Emtricitabine is a nucleoside reverse transcriptase inhibitor and is activity against HIV and HBV. Emtricitabine is approved for treatment of HIV infection [Emtriva (only Emtricitabine) and Truvada (in combination with tenofovir)], but it is not approved by FDA for HBV treatment. In patients with chronic hepatitis B, Emtricitabine contributes to histological, virological and biochemical improvement [48]. Side effects are infrequent (1%) and the most severe reported are lactic acidosis and hepatic failure [49].

Alcohol consumption should be avoided, because use of alcohol has been associated with deterioration of liver disease [50]. In naïve-patients with chronic hepatitis B, TAF, TDF and entecavir recommend be used as first line therapy because they are effective and have null (TAF, TDF) or low (entecavir) rates of resistance development.

Nucleosides analogue can be used during pregnancy. Tenofovir and telbivudine are characterized by FDA as pregnancy category B, and lamivudine, adefovir and entecavir as pregnancy category C.

The most important predictors of response to NAs are low viral load (HBV DNA < 2 X 10^8 IU/ml), high serum ALT levels and histological activity. HBV genotypes are not associated with NAs efficacy [51,52].

Treatment monitoring

On treatment: Patients, who treated with standard or pegylated interferon, should be monitored monthly with full blood counts and thyroid function (TSH) should be assessed every 12 weeks. At first year, HBV DNA should be measured every 12 weeks and every 24 weeks after one year. If patients are HBeAg positive, HBeAg and anti-HBeAg should be assessed every 24 weeks and when patients are HBeAg negative, HBsAg should be estimated every 24 to 48 weeks. ALT should be monitored every 12 weeks. Patients receiving adefovir or TDF should undergo periodical renal function monitoring.

After treatment: Initial, HBV DNA should be measured every 4 to 12 weeks and every 24 to 48 weeks after one year. If patients are HBeAg positive, HBeAg and anti-HBeAg should be assessed every 4 to 12 weeks at first year and then every 24 to 48 weeks, and when patients are HBeAg negative, HBsAg should be estimated every 48weeks. ALT should be monitored every 12 weeks.

Treatment endpoints

The ideal endpoint is HBsAg loss but it is difficult to achieve with available drugs, so more realistic endpoints are established such as HBeAg seroconversion and biochemical response. The endpoints differ depending on the case.

HBeAg positive chronic hepatitis B: Endpoint is HBeAg seroconversion, undetectable HBV DNA (< 2000 IU/ml) and normal ALT. Treatment NAs should be continued for at least 12 months after HBeAg seroconversion. Monitoring is essential after stop of treatment due to viral relapse

HBeAg negative chronic hepatitis B: The endpoint of therapy is not defined. Treatment should be continued until achieving HBsAg clearance. The most patients will need long term treatment because seroconversion HBsAg occurs infrequently. In HBeAg patients, tenofovir or entecavir are preferred because they have high barrier resistance. Adefovir is not preferred due to weak antiviral activity and low barrier of resistance after first year.

Compensated cirrhosis: These patients require long-term therapy. Treatment assists to prevent HCC and liver failure. Tenofovir and entecavir are preferred due to minimal risk of resistance. Interferon should not be used due to risk of bacteraemic infection.

Decompensated cirrhosis: Long-term treatment is recommended [53].

HCC screening

According to AASLD Practice Guidelines, ultrasound examination is recommended every 6 - 12 months and a-FP when US is not available in patients at high risk for HCC, regardless of the outcome of treatment [54]. HBV carriers at high risk are: persons with cirrhosis,

persons with a family history of HCC, any carrier over 40 years with persistent or intermittent ALT elevation and/or high HBV DNA level > 2000 IU/ml, African over 20 years age, Asian men over 40 years, Asian women over 50 years, patients with coexistence of HIV and patients waiting liver transplantation [54].

Prevention

There are two types prophylaxis against HBV infection: active immunization using inactive HBsAg (HBV vaccine) and passive immunization using hepatitis B immune globulin (HBIG). The vaccine contains only HBsAg and anti-HBs is the sole produced antibody. The hepatitis B vaccine is recommended for all infants and children up to age 18 years. The typical vaccination schedule is 0, 1 and 6 months. The most frequently reported side effects are pain at the injection side and fever. Also, the following persons, who are negative for anti-HBc and HBsAg, should be vaccinated: people with HIV infection, health care workers, people with chronic liver and kidney disease, persons with traveling to a country with moderate to high rates of HBV, sexual and household contacts of carriers [55]. Newborns of HBsAg positive mothers should be receive immunoprophylaxis (HBIG) and hepatitis B vaccine series should immediately initiate after delivery. This intervention is 95% efficacious in the prevention of perinatal transmission [56].

Extrahepatic manifestations

Several extrahepatic manifestations have been observed in patients with HBV infection and the cause of these manifestations is believed to base on immune complex reactions.

Arthritis-Dermatitis: The serum-sickness like ''arthritis-dermatitis'' is seen approximately in one third of patients with HBV infection [57] and should be distinguished from other disorders, because immunosuppressive therapy, if mistakenly given, can cause increases in viral replication and withdrawal of these agents has been associated with exacerbation of hepatitis [58].

Polyarteritis Nodosa: Polyarteritis Nodosa (PAN) is a necrotizing vasculitis of medium sized and small arteries. Clinical symptoms include abdominal pain, fever, arthralgias, hypertension and rash. About 30% of patients with PAN have chronic hepatitis B, but less than 1% with chronic HBV infection have PAN [59]. The patients with HBV-related PAN should receive plasmapheresis and antiviral therapy [60].

Glomerulonephritis: Infection with HBV may be associated with several types of glomerular lesions. The most common are membranous glomerulonephritis and membranoproliferative glomerulonephritis and the most common manifestation is the nephrotic syndrome. The diagnosis is established by presence of an immune complex glomerulonephritis and immunohistochemical localization of 1 or more HBV antigens in a renal biopsy specimen [61]. Lamivudine treatment has associated with improved renal function and reduction in proteinuria [62]. Therapy with interferon-a has also resulted in long term remission in liver disease [63].

Cryoglobulinemia: Type II and type III cryoglobulinemia have associated with HBV infection, but the association is very rare. Cryoglobulinemia may be asymptomatic or manifest as vasculitis (porpura, arthralgias and impairment of kidneys and peripheral nervous system). Nucleos(t)ide analogs have been used successfully in treatment of HBV-related cryoglobulemic vasculitis [64].

Conclusion

In conclusion, despite the development of vaccines and implementation of programs prevention, hepatitis B remains a worldwide health problem. The treatment of chronic hepatitis B is difficult, long term and requires the correct choice of antiviral agent, depending on the level of liver and renal function and the tolerance of possible side effects. Furthermore, patient should be monitored for adverse effects of therapy and possible extrahepatic manifestations of HBV infection.

Conflict of Interest

Authors declare no conflict of interest. No funding was received for this work.

Bibliography

1. Alter MJ. "Epidemiology of hepatitis B in Europe and worldwide". *Journal of Hepatology* 39.1 (2003): S64-S69.

2. Lavanchy D. "Worldwide epidemiology of HBV infection, disease burden, and vaccine prevention". *Journal of Clinical Virology* 34.1 (2005): S1-S3.

3. Ott JJ., *et al*. "Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity". *Vaccine* 30.12 (2012): 2212-2219.

4. Fonseca JC. "[Natural history of chronic hepatitis B]". *Revista da Sociedade Brasileira de Medicina Tropical* 40.6 (2007): 672-677.

5. Fattovich G. "Natural history of hepatitis B". *Journal of Hepatology* 39.1 (2003): S50-S58.

6. Terrault NA., *et al*. "AASLD guidelines for treatment of chronic hepatitis B". *Hepatology* 63.1 (2016): 261-283.

7. Kumar A., *et al*. "Clinical profile, genotype and management updates of hepatitis B virus". *Indian Journal of Virology* 22.1 (2011): 1-10.

8. Flink HJ., *et al*. "Treatment with Peg-interferon alpha-2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype". *American Journal of Gastroenterology* 101.2 (2006): 297-303.

9. Buster EH., *et al*. "Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa". *Gastroenterology* 137.6 (2009): 2002-2009.

10. Chan HL., *et al*. "Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma". *Gut* 53.10 (2004): 1494-1498.

11. Fung SK and AS Lok. "Hepatitis B virus genotypes: do they play a role in the outcome of HBV infection?" *Hepatology* 40.4 (2004): 790-792.

12. Lok AS and BJ McMahon. "Chronic hepatitis B: update 2009". *Hepatology* 50.3 (2009): 661-662.

13. Shiffman ML. "Management of acute hepatitis B". *Clinical Liver Disease* 14.1 (2010): 75-91.

14. Schmilovitz-Weiss H., *et al*. "Lamivudine treatment for acute severe hepatitis B: a pilot study". *Liver International* 24.6 (2004): 547-551.

15. Kondili LAH Osman and D Mutimer. "The use of lamivudine for patients with acute hepatitis B (a series of cases)". *Journal of Viral Hepatitis* 11.5 (2004): 427-431.

16. Castera L. "Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis". *Journal of Viral Hepatitis* 16.5 (2009): 300-314.

17. Myers RP., *et al*. "Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B". *Journal of Hepatology* 39.2 (2003): 222-230.

18. Hadziyannis SJ. "Review: hepatitis delta". *Journal of Gastroenterology and Hepatology* 12.4 (1997): 289-298.

19. Farci and GA Niro. "Clinical features of hepatitis D". *Seminars in Liver Disease* 32.3 (2012): 228-236.

20. Niro GA., *et al*. "Outcome of chronic delta hepatitis in Italy: a long-term cohort study". *Journal of Hepatology* 53.5 (2010): 834-840.

21. European Association for the Study of the Liver. Electronic address, e.e.e. and L. European Association for the Study of the, EASL 2017. "Clinical Practice Guidelines on the management of hepatitis B virus infection". *Journal of Hepatology* (2017).

22. Perrillo R. "Benefits and risks of interferon therapy for hepatitis B". *Hepatology* 49.5 (2009): S103-S111.

23. Kozielewicz D A Zalesna and D Dybowska. "Can pegylated interferon alpha 2a cause development of thyroid disorders in patients with chronic hepatitis B?" *Expert Opinion on Drug Safety* 13.8 (2014): 1009-1014.

24. Fried MW., *et al*. "HBeAg and hepatitis B virus DNA as outcome predictors during therapy with peginterferon alfa-2a for HBeAg-positive chronic hepatitis B". *Hepatology* 47.2 (2008): 428-434.

25. Flink HJ., *et al*. "Flares in chronic hepatitis B patients induced by the host or the virus? Relation to treatment response during Peg-interferon {alpha}-2b therapy". *Gut* 54.11 (2005): 1604-1609.

26. Dienstag JL., *et al*. "Lamivudine as initial treatment for chronic hepatitis B in the United States". *New England Journal of Medicine* 341.17 (1999): 1256-1263.

27. Hadziyannis SJ., *et al* "Efficacy of long-term lamivudine monotherapy in patients with hepatitis B e antigen-negative chronic hepatitis B". *Hepatology* 32 (2000): 847-851.

28. Marcellin P., *et al*. "Long-term efficacy and safety of adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B". *Hepatology* 48.3 (2008): 750-758.

29. Hadziyannis SJ., *et al*. "Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B". *New England Journal of Medicine* 348.9 (2003): 800-807.

30. Luo Q., *et al*. "Relationship between nephrotoxicity and long-term adefovir dipivoxil therapy for chronic hepatitis B: A meta-analysis". *Medicine (Baltimore)* 95.50 (2016): e5578.

31. Girgis CM., *et al*. "Hypophosphataemic osteomalacia in patients on adefovir dipivoxil". *Journal of Clinical Gastroenterology* 45.5 (2011): 468-473.

32. Lai CL., *et al* "Telbivudine versus lamivudine in patients with chronic hepatitis B". *New England Journal of Medicine* 357.25 (2007): 2576-2588.

33. Chan HL., *et al*. "Renal Function in Nucleos(t)ide Analog-Treated Patients with Chronic Hepatitis B: A Systematic Literature Review and Network Meta-Analysis". *Advances in Therapy* 33.5 (2016): 862-875.

34. Gane EJ., *et al*. "Telbivudine improves renal function in patients with chronic hepatitis B". *Gastroenterology* 146.1 (2014): 138-146.

35. Zou XJ., *et al*. "Clinical features and risk factors of creatine kinase elevations and myopathy associated with telbivudine". *Journal of Viral Hepatitis* 18.12 (2011): 892-896.

36. Xu H., *et al*. "Lamivudine/telbivudine-associated neuromyopathy: neurogenic damage, mitochondrial dysfunction and mitochondrial DNA depletion". *Journal of Clinical Pathology* 67.11 (2014): 999-1005.

37. Tenney., DJ., *et al*. "Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to Lamivudine". *Antimicrobial Agents and Chemotherapy* 48.9 (2004): 3498-507.

38. Chang TT., *et al* "A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B". *New England Journal of Medicine* 354.10 (2006): 1001-1010.

39. Sherman M., *et al*. "Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks". Hepatology 48.1 (2008): 99-108.

40. Lange CM., *et al*. "Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function". *Hepatology* 50.6 (2009): 2001-2006.

41. Marcellin P., *et al*. "Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B". *New England Journal of Medicine* 359.23 (2008): 2442-2455.

42. Snow-Lampart A., *et al*. "No resistance to tenofovir disoproxil fumarate detected after up to 144 weeks of therapy in patients monoinfected with chronic hepatitis B virus". *Hepatology* 53.3 (2011): 763-773.

43. Gracey DM., *et al*. "Tenofovir-associated Fanconi syndrome in patients with chronic hepatitis B monoinfection". *Antiviral Therapy* 18.7 (2013): 945-948.

44. Magalhaes-Costa P., *et al*. "Fanconi syndrome and chronic renal failure in a chronic hepatitis B monoinfected patient treated with tenofovir". *Revista Espanola De Enfermedades Digestivas* 107.8 (2015): 512-514.

45. European Association for the Study of the Liver. "EASL clinical practice guidelines: Management of chronic hepatitis B virus infection". *Journal of Hepatology* 57.1 (2012): 167-185.

46. Scott LJ and HLY Chan. "Tenofovir Alafenamide: A Review in Chronic Hepatitis B". *Drugs* 77.9 (2017): 1017-1028.

47. Custodio JM., *et al*. "Pharmacokinetics and Safety of Tenofovir Alafenamide in HIV-Uninfected Subjects with Severe Renal Impairment". *Antimicrobial Agents and Chemotherapy* 60.9 (2016): 5135-5140.

48. Lim SG., *et al*. "A double-blind placebo-controlled study of emtricitabine in chronic hepatitis B". *Archives of Internal Medicine* 166.1 (2006): 49-56.

49. Margolis AM., *et al*. "A review of the toxicity of HIV medications". *Journal of Medical Toxicology* 10.1 (2014): 26-39.

50. Villa E., *et al*. "Susceptibility of chronic symptomless HBsAg carriers to ethanol-induced hepatic damage". *Lancet* 2.8310 (1982): 1243-1244.

51. Kweon YO and KH Kang. "[Pretreatment ALT level and histologic activity as predictors of HBeAg loss in lamivudine treatment for chronic hepatitis B]". *Korean Journal of Hepatology* 10.1 (2004): 31-41.

52. Perrillo RP., *et al*. "Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B". *Hepatology* 36.1 (2002): 186-194.

53. Peng CY., *et al*. "Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy". *Journal of Hepatology* 57.2 (2012): 442-450.

54. Bruix J., *et al*. "Management of hepatocellular carcinoma". *Hepatology* 42.5 (2005): 1208-1236.

55. Mast EE., *et al*. "A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults". *MMWR Recommendations and Reports* 55 (2006): 1-33.

56. Mast EE., *et al*. "A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents". *MMWR Recommendations and Reports* 54 (2005): 1-31.

57. Baig S and M Alamgir. "The extrahepatic manifestations of hepatitis B virus". *Journal of College of Physicians and Surgeons Pakistan* 18.7 (2008): 451-457.

58. Manzano-Alonso ML and G Castellano-Tortajada. "Reactivation of hepatitis B virus infection after cytotoxic chemotherapy or immunosuppressive therapy". *World Journal of Gastroenterology* 17.12 (2011): 1531-1537.

59. Kappus MR and RK Sterling. "Extrahepatic manifestations of acute hepatitis B virus infection". *Gastroenterology and Hepatology (NY)* 9.2 (2013): 123-126.

60. Schirmer JH., *et al*. "[Polyarteritis nodosa: differential diagnostics and therapy]". *Zeitschrift für Rheumatologie* 73.10 (2014): 917-927.

61. Venkataseshan VS., *et al*. "Hepatitis-B-associated glomerulonephritis: pathology, pathogenesis, and clinical course". *Medicine (Baltimore)* 69.4 (1990): 200-216.

62. Tang S., *et al*. "Lamivudine in hepatitis B-associated membranous nephropathy". *Kidney International* 68.4 (2005): 1750-1758.

63. Conjeevaram HS., *et al*. "Long-term outcome of hepatitis B virus-related glomerulonephritis after therapy with interferon alfa". *Gastroenterology* 109.2 (1995): 540-546.

64. Mazzaro C., *et al*. "Hepatitis B virus related cryoglobulinemic vasculitis: A multicentre open label study from the Gruppo Italiano di Studio delle Crioglobulinemie – GISC". *Digestive and Liver Disease* 48.7 (2016): 780-784.

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