Management of Hepatitis B Virus (HBV) Infection: Executive Summary: 2018 Guidelines from the Canadian Association for the Study of the Liver (CASL) and Association of Medical Microbiology and Infectious Disease (AMMI) Canada

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KEY POINTS

1. Hepatitis B virus infection is an important public health problem in Canada and individuals at risk should be screened for infection
2. All Canadian Provinces and Territories should offer universal neonate (preferable) / infant HBV vaccination
3. All patients with hepatitis B should be monitored and, as per age / risk based guidelines patients should undergo surveillance for liver cancer (hepatocellular carcinoma)
4. Hepatitis B can be treated with effective oral antiviral therapy (i.e, nucleos(t)ide analogues) or in carefully selected patients with subcutaneous Interferon (Pegylated-Interferon) to reduce the risk of liver disease progression

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BOX 1. SUMMARY OF RECOMMENDATIONS FOR MANAGEMENT OF HEPATITIS B INFECTION

Recommendations for HBV Diagnosis and Prevention:

1. Health Canada, The Public Health Agency and the provinces and territories should increase support and development of uniform structural programs for hepatitis B to: (a) prevent HBV infection (b) identify infections (screening especially in high risk groups, including all candidate immigrants) and (c) facilitate the assessment, treatment and education of chronically infected patients. (strong recommendation, class 2, level B)
2. All Canadian provinces and territories should harmonize the hepatitis B vaccination policy with universal, preferably neonatal, or infant vaccination with catch-up vaccinations for those who have not yet received adolescent vaccination. (strong recommendation, class 3)
3. Routine booster doses of HBV vaccine are not indicated in average-risk, immune-competent individuals who responded to the primary series of vaccine. (strong recommendation, class 2, level A)
4. A repeat series (three doses of vaccine) should be offered to those at high risk of exposure and/or those that are immunosuppressed and who do not respond to the first series of vaccines. (strong recommendation, class 1)
5. All high-risk individuals should be screened for HBV infection with HBsAg, anti-HBs, and anti-HBc, and their response to the vaccine should be assessed. (strong recommendation, class 2, level B)
6. All high-risk individuals who are HBsAg, anti-HBc, and anti-HBs negative should receive the HBV vaccine, and their response to the vaccine should be assessed. (strong recommendation, class 1)

Recommendations for Monitoring of Untreated Chronic Hepatitis B (CHB) Infection

7. All CHB (HBsAg-positive) patients must be assessed including a physical exam for signs of chronic liver disease, testing for baseline liver biochemistry (ALT), complete blood count, creatinine, HBV

DNA, HBeAg serology, and for fibrosis (either non-invasive assessment or liver biopsy). All should be evaluated for co-morbid liver disease (i.e., hepatitis C), and screening for HIV and hepatitis delta virus (HDV) in high risk groups (i.e., persons who inject drugs (PWID), immigrant from endemic areas) should be considered. (strong recommendation, class 2, level A)

8. All CHB carriers should have regular monitoring of ALT (every 6 months) and HBV DNA (every 6–12 months), or at less frequent intervals, depending on individual baseline assessment and risk of liver disease progression. (strong recommendation, class 2, level A)

9. Repeat fibrosis assessment may be indicated if persistent ALT elevation and HBV DNA are present to assess the need for treatment. (strong recommendation, class 3)

Recommendations for HCC surveillance in HBV infected Individuals

10. Abdominal ultrasound screening every 6 months is recommended in the following patients with chronic HBV infection. Serum AFP monitoring is not recommended for HCC screening if US is available. (strong recommendation, class 2, level B)
    a. Asian male aged 40 years or older
    b. Asian female aged 50 years or older
    c. Persons of African origin aged 20 years or older (due to risk of HCC even in non-cirrhotic patients)
    d. All cirrhotic patients irrespective of age
    e. Family history of hepatocellular carcinoma (in first degree relative(s))
    f. All HIV-co-infected patients (starting at age 40)

Recommendations for HBV Laboratory Testing

11. Clinicians should have access to regular HBV serological (i.e., HBsAg, HBeAg) and quantitative HBV DNA testing to assist in patient management. (strong recommendation, class 1)

12. Specialized mutation and genotype testing, may be used selectively by specialists to help direct treatment and management decisions. (moderate recommendation, class 2, level B)

13. Serological testing should be available from regional or provincial laboratories, while molecular testing should be available through provincial laboratories or reference laboratories (the *Guide to Services* provided by the National Microbiology Laboratory can be found at https://cnphi.canada.ca/gts/faces/public/index.xhtml). (moderate recommendation, class 2, level C)

14. As evidence becomes available for the clinical utility of new tests to provide surrogate measures of HBV replication and the presence of cccDNA, these tests should be considered for incorporation into provincial and/or reference laboratories. (weak recommendation, class 3)

Recommendations for HBV Treatment

15. HBeAg–positive (phase 2) and HBeAg–negative (phase 4) patients in whom the HBV DNA is > 2,000 IU/mL with elevated ALT (> 1 X ULN) for 3–6 months should be considered for treatment (strong recommendation, class 2, level A)

16. Patients with significant inflammation or fibrosis (> above stage 1) should be considered for treatment, even if HBV DNA is lower than 2,000 IU/mL, or the ALT is normal (strong recommendation, class 2, level A)

17. All patients with cirrhosis and detectable HBV DNA should be treated regardless of HBV DNA (strong recommendation, class 2, level A)

18. TAF, TDF or ETV is first line therapy for treatment-naïve HBV patients because they are the most potent agents available with no or very low rates of antiviral resistance (strong recommendation, class 1)

19. TDF or TAF is first line therapy for LAM -resistant HBV. ETV should not be used in this case because of the risk of development of ETV resistance (strong recommendation, class 1)

20. A weekly dose of 180 µg PEG-IFN alpha 2a for 48 weeks may be used to treat non-cirrhotic HBeAg–positive CHB. (moderate recommendation, class 1)

21. A weekly subcutaneous dose of 180 µg of Peg-IFN alpha 2a in combination with TDF given for 48 weeks may be used to treat CHB in the absence of advanced fibrosis. (moderate recommendation, class 1)

22. The target HBV DNA level while patients are on oral NA therapy is undetectable, measured using the most sensitive test available (i.e., currently Taqman PCR). (strong recommendation, class 2, level A)
23. In HBeAg positive patients who achieve HBeAg seroconversion with NA treatment, a minimum of 12 months of additional consolidation therapy is required in order to maximize the durability of the response before considering treatment cessation, with close monitoring for relapse thereafter. Alternatively, treatment may be continued until HBsAg loss. (moderate recommendation, class 2, level B)
24. In HBeAg negative patients receiving NA, treatment should continue until HBsAg loss. (moderate recommendation, class 2, level B)
25. HBeAg–positive individuals receiving Peg-IFN alpha who have HBsAg of more than 20,000 IU/mL at week 24 should discontinue therapy because of the low probability of response. (strong recommendation, class 2, level B)
26. All persons with cirrhosis or HCC should be treated with NA until HBsAg loss or indefinitely. (moderate recommendation, class 2, level B)
27. Patients must continue to be screened for HCC as per current guidelines irrespective of response to antiviral treatment. (strong recommendation, class 2, level B)

Recommendations for Management of HBV Antiviral Resistance

28. If a patient receiving NA therapy is confirmed to be treatment adherent has increasing HBV DNA (virologic breakthrough), salvage therapy should be introduced (strong recommendation, class 1)
29. Antiviral resistance testing should be used to differentiate between non-adherence and the emergence of resistant virus in patients with virologic breakthrough or persistent viremia (moderate recommendation, class 2, level B).
30. HBV DNA should initially be monitored every 3 months to allow early detection of viral resistance, and every 6–12 months once aviremia is achieved if on highly potent NA, or every 3 months if the patient is on LAM. (strong recommendation, class 2, level B).
31. The treatment of choice for LAM-resistant HBV infection is to switch to TDF (strong recommendation, class 1).

Recommendations for Management of HBV and Pregnancy

32. All pregnant women should be screened for HBsAg in the first trimester of pregnancy. (strong recommendation, class 1)
33. HBsAg-positive pregnant women should undergo additional assessment with HBeAg, anti-HBe, HBV DNA and ALT and be referred to a specialist for management. (strong recommendation, class 1)
34. TDF is the drug of choice in pregnant women and women of childbearing potential who require immediate treatment of HBV. (strong recommendation, class 1)
35. For women planning to become pregnant, who have indications for therapy and favourable predictors of response (low HBV DNA, high ALT, genotype A), Peg-IFN for 48 weeks can be considered for those who are willing to defer pregnancy to undertake therapy of finite duration (as is recommended for all chronic carriers who wish to consider finite therapy). (moderate recommendation, class 2, level B)
36. Pregnant women with HBV DNA of more than 200,000 IU/mL should initiate antiviral therapy at 24–32 (~28) weeks of gestation to reduce the risk of vertical transmission; TDF is the drug of choice and may be stopped at delivery or up to 4–8 weeks postpartum if given strictly to prevent MTCT. (strong recommendation, class 1)
37. All women should be monitored for ALT flares post-partum with ALT every 4 weeks for the first 3 months, then at 6 months, followed by routine monitoring thereafter, (moderate recommendation, class 2, level B)
38. All infants born to HBsAg positive mothers should receive immunoprophylaxis with HBIg and HBV vaccine within 12 hours of birth and completion of second and third HBV vaccine doses at ~1 and 6 months, respectively. (strong recommendation, class 1)
39. Babies should be tested with HBsAg and anti-HBs between 1 and 4 months after the last dose of vaccine to confirm they are uninfected and immune. (strong recommendation, class 2, level A)

40. Breastfeeding is not contraindicated in either untreated HBsAg positive mothers or those on NA. (strong recommendation, class 1)

Recommendations for Management of Health Care Workers (HCW) with Hepatitis B

41. All HCWs who perform EPPs as defined by the US Centers for Disease Control and Prevention (procedures performed on a difficult to access area with limited visualization and significant risk of puncture to the HCW) have an ethical obligation to know their HBV status. (strong recommendation, class 2)
42. All susceptible HCWs, including students, should be immunized for HBV. (strong recommendation, class 1)
43. HBV infection alone should not disqualify an infected person from study or practice in any field of healthcare. (strong recommendation, class 2, level C)
44. HCWs infected with HBV should be under the care of an independent physician with expertise in the management of HBV. (moderate recommendation, class 2, level B)
45. HCWs infected with HBV who do not perform EPPs do not need restrictions placed on their practice. (moderate recommendation, class 2, level B)
46. HCWs infected with HBV should be restricted from performing EPPs if their HBV DNA is above 1,000 IU/mL. (moderate recommendation, class 2, level B)
47. For HCWs infected with HBV who perform EPPs, consideration should be given to treating at any viral load, after a discussion of the potential risks and benefits, given the common fluctuations in HBV DNA in untreated individuals and the risk of interruption of practice should this occur. (moderate recommendation, class 3)
48. HCWs infected with HBV who perform EPPs should have HBV DNA monitored every 3–6 months regardless of whether or not they are on antiviral therapy. (moderate recommendation, class 2, level B)
49. HCWs infected with HBV must follow routine IPC practices to minimize the risk of transmission and report any potential patient exposure in their workplace/facility. (strong recommendation, class 2, level A)

Recommendations for Management of Hepatitis B in Immunosuppressed Patients

50. All patients undergoing immunosuppression or chemotherapy should be screened for HBsAg, anti-HBc and anti-HBs before therapy. (strong recommendation, class 2, level A)
51. HBsAg-positive patients are at high risk of reactivation and should undergo either close monitoring or prophylactic NA therapy (especially with moderate-potent immunosuppression). (strong recommendation, class 2, level A)
52. HBsAg-negative, anti-HBc positive patients may be at risk of reactivation and, based on their degree of risk should undergo either close monitoring (if high anti-HBs titres > 100–1,000 IU/L) or prophylactic NA therapy (especially if they are on B cell depleting therapies or about to undergo hematopoietic stem cell transplant). (moderate recommendation, class 2, level C)
53. Potent NAs (ETV, TDF or TAF) are preferred when prophylaxis is used; LAM is an alternative especially in HBsAg negative, anti-HBc positive cases. (strong recommendation, class 2, level A)
54. After completion of immunosuppressive therapy, monitoring or prophylaxis as applicable, should continue for at least 12 months or until immune reconstitution, or longer in those who received B-cell depleting therapies. (strong recommendation, class 2, level B)

Recommendations for Management of Hepatitis B and Renal Disease

55. Biopsy-proven renal disease caused by CHB is an indication for hepatitis B treatment. (strong recommendation, class 1)
56. Renal function should be monitored every 6–12 months while on NA therapy, urine protein and glucose, and fasting phosphate should be monitored annually. (strong recommendation, class 2, level B)
57. Among patients with signs of worsening renal function (decline in eGFR) while on TDF, a switch to ETV or TAF is recommended. (strong recommendation, class 2, level A).

Recommendations for Management of Hepatitis B and Decompensated Cirrhosis

58. NA treatment of adults with HBsAg-positive decompensated cirrhosis should be initiated promptly, regardless of HBV DNA, HBeAg status, or ALT level. (strong recommendation, class 1)

59. Potent antiviral therapy with a NA with a low rate of drug resistance must be initiated. TDF or ETV are the preferred options. (strong recommendation, class 1)

60. TAF is a potential option in patients with decompensated cirrhosis, but long-term data on the safety of TAF in this population are lacking. (moderate recommendation, class 2, level B)

Recommendations for Management of Hepatitis B and Liver Transplantation

61. All HBV patients considered for liver transplantation should be treated with NAs. (strong recommendation, class 1)

62. A combination of HBIg and NAs (ETV or TDF) is the standard of care after liver transplant. (strong recommendation, class 2, level A)

63. In selected patients with a low risk of HBV recurrence, HBIg can be discontinued 6–12 months after transplant, while NAs are continued indefinitely. (moderate recommendation, class 2, level A)

64. HBsAg-negative transplanted patients receiving a liver from a donor with evidence of past HBV infection (i.e., anti-HBc positive, HBsAg negative) should receive lifelong prophylaxis with NAs. (strong recommendation, class 2, level A)

Recommendations for Management of Acute Hepatitis B Infection

65. More than 90–95% of immunocompetent adults with acute hepatitis B do not require specific treatment because they will fully recover spontaneously. (strong recommendation, class 2, level A)

66. Patients with severe or fulminant acute hepatitis B can be treated with NAs, especially if they are considered for liver transplantation. (strong recommendation, class 2, level C).

Recommendations for Management of HBV and HIV Coinfection

67. All people living with HIV should be screened for HBV infection and immunity. If an individual is anti-HBs and anti-HBc negative then HBV immunization should be pursued. (strong recommendation, class 2, level A)

68. HIV treatment with dual HBV-active antivirals should be initiated once the diagnosis of HIV and HBV is established and irrespective of CD4+ T cell count. (strong recommendation, class 2, level A)

69. On-treatment monitoring of HBV is the same as for people with HBV monoinfection, but HBV therapy is continued until HBsAg loss. (moderate recommendation, class 2, level C)

70. Patients who have interruptions in HIV therapy, that included dual-active HBV antivirals should be monitored for HBV reactivation if they are unable to continue with an anti-HBV antiviral. (strong recommendation, class 2, level B)

Recommendations for Management of HBV and HCV Coinfection

71. All HCV patients should be tested for HBsAg before DAA therapy is initiated. (strong recommendation, class 2, level B)

72. HBsAg positive patients should undergo monthly ALT and q 1–3-month HBV DNA monitoring while on HCV DAA and until 24-weeks post treatment. HBV antiviral therapy should be initiated promptly in patients with a rise in ALT and HBV DNA (> 1 log IU/mL) during or after completion of DAA therapy or if there is persistent cirrhosis at baseline. (moderate recommendation, class 2, level C)

73. HBsAg-negative and anti-HBc positive (with or without anti-HBs) patients should be monitored with ALT while on HCV DAA and until 24-weeks post-treatment. HBsAg and HBV DNA should be measured if ALT does not normalize or increases during or after completion of DAA treatment. HBV antiviral therapy should be initiated promptly in those that become HBsAg positive or show detectable HBV DNA with persistently elevated ALT. (moderate recommendation, class 2, level C)

Recommendations for Management of HBV and HDV Coinfection

74. HBV positive patients from HDV endemic areas, and/or have a history of injection drug use, have abnormal ALT despite antiviral therapy, and advanced liver disease should be screened for HDV co-infection. (strong recommendation, class 2, level B)

75. HDV screening should use an approved assay for HDV antibody detection followed by confirmatory HDV RNA by PCR. (strong recommendation, class 2, level B)
76. Peg-IFN therapy (180 µg once weekly) for 48 weeks should be considered in individuals without contraindications to IFN treatment. (moderate recommendation, class 1)
77. HBV should be monitored during Peg-IFN therapy, and anti-HBV NA should be considered to block residual viral replication, especially if patients are cirrhotic and given the risk of more aggressive liver disease progression. (moderate recommendation, class 3)
78. Research on HDV epidemiology, including detailed long-term natural history studies and new therapies is urgently needed. (strong recommendation, class 3)

Recommendations for Management of HBV in Pediatric Patients

79. There is no indication for treatment of children without complications in the immune-tolerant (phase 1) and inactive (phase 3) phases of chronic HBV infection. (moderate recommendation, class 2, level B)
80. Children with chronic HBV infection, either HBeAg positive or negative, should be followed once a year by ultrasound examination of the liver (and elastography or fibrosis assessment) and serum AFP, in addition to ALT and HBV DNA. (moderate recommendation, class 3)
81. In HBeAg positive children with ALT greater than 1.3–2 times ULN, monitoring every 3 months for at least 1 year, to document decreasing or low levels of serum HBV-DNA is recommended before considering treatment to allow for possible spontaneous seroconversion. (strong recommendation, class 2, level C)
82. Treatment should be considered in children with cirrhosis, extrahepatic disease and co-infection. (strong recommendation, class 2, level C)
83. ETV and TDF are drugs that are orally administered and exhibit a high genotypic barrier to resistance and a favourable side effect profile. Thus, ETV should be considered as first-line therapy for children older than age 3 years and TDF for those older than age 12 years. PEG IFN treatment may also be considered, which must be weighed against the significant side effects and potential impact on central nervous system development (strong recommendation, class 1, level A)
84. NA therapy should be continued for 1 year after the disappearance of HBeAg and the appearance of anti-HBe (seroconversion) before attempting cessation. (strong recommendation, class 1, level A)
85. After HBeAg seroconversion, whether spontaneous or treatment-induced, children should be followed every 3 months for at least 1 year. After confirmation of inactive carrier status (phase 3, persistently normal ALT, HBV DNA < 2,000 IU/ml), monitoring should be continued every 6 months. (strong recommendation, class 2, level B)

INTRODUCTION

Hepatitis B virus (HBV) infection is an important public health problem, thus the Canadian Association for the Study of the Liver (CASL) has periodically published HBV management guidelines in keeping with evolving evidence (1,2). The goals of the 2018 HBV guidelines are: (1) to highlight the public health impact of HBV infection in Canada, and the need to improve diagnosis and linkage to care, (2) recommend current best practise for treatment of HBV, (3) summarize the key HBV laboratory diagnostic tests and, (4) review evidence on HBV management in special patient populations. The aim of the guidelines is to serve as an up-to-date resource for health care providers in the management of HBV infection. The target audience is hepatologists, infectious disease specialists and other health care professionals involved in treating HBV infection.

METHODS

Representatives from two Canadian Medical Societies formed the guideline committee, i.e., CASL and Association of Medical Microbiologists and Infectious Disease Canada (AMMI). The Appraisal of Guidelines for Research & Evaluation (AGREE-II) was used to assess the quality of guidelines (www.agreetrust.org) (3). The strength and evidence for each recommendation was rated according to the Grades of Recommendation, Assessment Development and Evaluation (GRADE, www.gradeworkinggroup.org) (4) (Box 1). Each section was assigned to

one to three expert authors with discussion of alternatives, barriers and resource limitations as appropriate. All sections were reviewed by the writing committee and key recommendations subjected to vote and approval by the expert panel. The guidelines were disseminated for review and feedback to AMMI and CASL membership. A process for updating the guidelines includes application to the Chair of the CASL education committee, selection of the writing panel and obtaining membership feedback. All conflict of interests was submitted to the Chair of CASL guidelines committee and pre-approved. No funding was provided to develop these guidelines.

RECOMMENDATIONS

HBV Diagnosis and Prevention

There are an ~250 million chronic HBV (CHB) carriers worldwide and ~900,000 deaths annually from cirrhosis and hepatocellular carcinoma (HCC), with highest prevalence in the Western Pacific and African Regions (5,6). In Canada, hepatitis B is a reportable disease to the Canadian Notifiable Disease Surveillance System (CNDSS) (7). A recent assessment estimated ~250,000–460,000 individuals with CHB in Canada, with highest rates in British Columbia, Ontario and Alberta (23.4, 15.1 and 14.6 per 100,000, respectively) (8). CHB mostly affects

individuals that have not received routine immunization, and/or are immigrants from endemic countries; in one study non-Canadian born children had 12 times higher relative risk for CHB (9). In adults, risk factors include having a chronic carrier as a family member, injection drug use, high-risk sexual activity, body piercing/tattooing, and history of blood transfusion (10). As reported in the Ontario Burden of Infectious Diseases Study, CHB was the fifth-ranked pathogen causing significant health adjusted life years lost (11). Modelling data show that immigrants with CHB lost an average of 4.6 life years with higher lifetime risk of end-stage liver disease (12). CHB is often asymptomatic and screening is important to identify individuals at risk. (Box 2).

Reducing the disease burden of CHB is contingent upon HBV vaccination. HBV vaccine candidates include all children and adolescents as well as high risk individuals (Box 1) (13). Although, the national childhood HBV coverage for > 1 dose of the vaccine was 87.9% in 2013 (14), the prevalence of vaccine induced immunity was < 30% for the age group over 30 (15). As the likelihood of developing CHB is greatest when exposure occurs in early childhood, universal vaccination should be offered to all neonates or infants. Worldwide, the incidence of childhood CHB has fallen from 4.7% to 1.3% in 2015 through this strategy (6). However,

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BOX 2: SCREENING RECOMMENDATIONS FOR HEPATITIS B IN PERSONS NOT KNOWN TO BE HBV IMMUNE / VACCINATED. HIGH RISK INDIVIDUALS THAT TEST HEPATITIS B SURFACE ANTIGEN (HBSAG) AND HBV SURFACE ANTIBODY (ANTI-HBS) NEGATIVE SHOULD BE OFFERED THE VACCINE.

1. Born or resident in region where HBV is more common (Central, East, South Asia, Australasia, Eastern Europe, South America, Sub-Saharan Africa, North Africa/Middle East)
2. Household contacts of HBV carriers (including unvaccinated persons whose parents were from HBV-endemic countries) especially children of HBV positive mothers
3. Sexual contacts of HBV carriers, persons with multiple sexual partners
4. Illicit injection or intranasal drug use or shared drug paraphernalia (past or present)
5. Inmates
6. Patients with chronic renal failure needing dialysis
7. Signs of liver disease (i.e. abnormal liver enzyme tests) or other infectious diseases (i.e.: hepatitis C, HIV, etc.). (Hepatomegaly, splenomegaly, thrombocytopenia and jaundice are late findings)
8. All pregnant women
9. Patients needing immune modulation therapy or those who will develop immunosuppression such as cancer chemotherapy

Adapted from the Canadian Liver Foundation, www.liver.ca and Public Health Agency of Canada National Immunization Guide

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only New Brunswick, Nunavut and the Northwest Territories provide HBV vaccination to newborns at birth, British Columbia and Quebec, and Alberta (since September 2018) provide at 2 months. Other Canadian jurisdictions vaccinate for HBV in preadolescence, unless the neonates are deemed to be at-risk through maternal screening for hepatitis B surface antigen (HBsAg). These public health disparities highlight the need for a harmonized national HBV vaccination schedule.

HBV Monitoring

The outcome of acute hepatitis B is impacted by patient age and immune status (Tables 2–3). In adults, acute HBV is usually self-limited, but < 1% can develop fulminant liver failure, and ~5% may develop CHB with HBsAg persistence > 6 months. Most infants or young children acquire HBV vertically (mother to infant) in the peripartum period or horizontally via unrecognized contact with infectious body fluids of close household contacts (9). CHB is a dynamic disease influenced by the interplay between the virus and host immune responses (16). Recent studies have shown HBV specific T cell responses in young immune tolerant individuals (17,18), and that inactive CHB carriers may be at risk of HCC (19). Thus, a revised terminology has been adopted to highlight the dynamic nature of CHB (Table 3) (20–22). CHB carriers have ~25% lifetime risk of cirrhosis or HCC, which correlates with the severity of liver injury, viral load, infection duration, male gender, and concomitant

Table 1: Guideline development using the Grade (grades of recommendation, assessment development and evaluation) Scale (level of evidence) according to study design

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case controlled studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinion of respected authorities. Descriptive epidemiology

www.gradeworkinggroup.org
Notes: Each recommendation was based on quality of the supporting evidence/study design and graded as Class / Grade: 1 (high), 2-A, 2-B, 2-C (moderate), or 3 (low) quality evidence

liver diseases, and rarely cause extrahepatic syndromes (23). Thus, all HBsAg+ patients should be monitored.

HBV Hepatocellular Carcinoma (HCC) Surveillance

The annual incidence of HCC in non-cirrhotic HBV-infected individuals is 0.5% in Asians, 0.2% in Alaskan natives and ~0.3% in Caucasians (23,24), but is unclear in Africans or North Americans blacks due to limited data. In cirrhotics, HCC incidence is ~2–3% / year, with a 5-year incidence of 15–20% (25). Known risk factors are age > 40, male, immunocompromise, family history, cirrhosis, high HBV DNA (> 2,000 IU/mL), elevated ALT, prolonged time to HBeAg seroconversion, genotype C, coinfection with hepatitis C virus (HCV), hepatitis Delta (HDV), human immunodeficiency virus (HIV); heavy alcohol use, non-alcoholic fatty liver disease, and smoking (23). HBsAg titres may correlate with HCC risk in patients with low level viremia (26). Serum alpha-fetoprotein (AFP) was utilized as a tumour marker, but HCC can occur with normal AFP (27). Scoring systems have been developed (mainly in Asian cohorts), to predict HBV-related HCC, including the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer- (REVEAL-HBV) (28) and a nomogram using five predictors of HCC based on the Risk Estimation for HCC in CHB study (REACH-B) (29). The PAGE-B score based on platelets, age and gender, was validated in Caucasian CHB patients on antivirals (30). The Toronto HCC risk index was developed to predict the 10-year risk of HCC in cirrhotic patients and is the first Canadian scoring system using readily available clinical parameters to risk-stratify patients (31). Surveillance leads to an increase in detection of early stage HCC amenable to curative therapy and improves survival. Biannual liver ultrasound is recommended for HCC screening and the 6-month interval was selected based on tumour doubling time and cost-effectiveness analyses (32).

HBV Laboratory Testing

HBV serological markers (antigens and antibodies) diagnose infection and help identify the phase of infection, while molecular markers (HBV DNA, covalently closed circular (ccc)-DNA) indicate viral replication and persistence (Table 2). HBV cccDNA persists in the liver cell despite HBsAg loss or treatment-induced HBV DNA suppression, hence patients remain susceptible to reactivation and HCC (33). HBV DNA quantification is used to guide

Table 2: Summary of HBV serological tests

| | Anti-HBs | Anti-HBc | | Anti-HBe | HBsAg | HBeAg |
		IgM	IgG/IgM total			
Immunization	A marker of immunization. Anti-HBs will be the sole seromarker present (with history of immunization)					
Acute infection		A marker of acute infection. May also indicate severe acute exacerbation of chronic infection, thus requiring clinical/ epidemiological history to distinguish			A marker of infection/ infectivity	
Previous or current (chronic) infection	A marker of previous infection (following seroconversion and in association with the presence of other HBV antibodies)		A marker of previous or current infection, depending on the presence of other serological and molecular markers of HBV infection. The presence of anti-HBc in isolation is associated with occult hepatitis B (OHB).	A marker of chronic infection indicating the phase of infection*	When positive ≥ 6 months a marker of chronic infection	A marker of viral replication and infectivity indicating the phase of infection*

* *HBeAg positive, anti-HBe negative: characterized by high HBV DNA and normal ALT (Phase 1) or elevated/fluctuating ALT levels (Phase 2); HBeAg negative, anti-HBe positive: indicates the inactive carrier phase of chronic hepatitis associated with low HBV DNA and normal ALT levels (Phase 3) or it indicates HBeAg negative chronic hepatitis in the context of fluctuating HBV DNA and ALT levels, often due to the presence of mutations reducing or eliminating HBeAg expression (Phase 4), according to the revised classification system*

treatment and indicate the phase of infection. Persistently high HBV DNA levels are a risk factor for liver disease (28), increasing HBV DNA while on treatment (especially with first generation NA) can indicate antiviral resistance vs. noncompliance. Occult hepatitis B (OHB) defined as the presence of HBV DNA in serum or liver in the absence of detectable HBsAg (34), has been associated with liver disease and risk of HCC. OHB may lead to reactivation of resolved infection (anti-HBc positive, with or without anti-HBs antibody, and HBsAg negative), particularly during immunosuppressive therapy or treatment of HCV co-infection with direct acting antivirals (DAA). HBsAg quantification (qHBsAg) is a recent marker reflecting CHB natural history, with putative cut-off values (35) associated with fibrosis risk in treatment-naïve HBeAg+ CHB, depending on genotype and ALT. Similarly, qHBsAg levels < 100 IU/mL could signify immune control and inactive disease (36). Stopping rules for HBeAg+ and HBeAg– patients treated with PEG IFN have been established (37). The effect of NA treatment on HBsAg kinetics is less pronounced as NA do not inhibit cccDNA. However, in HBeAg negative patients on

Table 3: Phases of chronic HBV infection according to revised and classical definitions

	Phase 1 HBeAg + Chronic Infection, (Old terminology Immune Tolerance)	Phase 2 HBeAg+ Chronic Hepatitis, (Old terminology Immune Active)	Phase 3 HBeAg–Chronic Infection, (Old terminology Inactive Carrier)	Phase 4 HBeAg –Chronic Hepatitis (Old terminology, HBeAg–negative Chronic Hepatitis)	Phase 5 HBsAg negative/ Occult Hepatitis B, OHB
HBsAg	Positive	Positive	Positive	Positive	Negative
HBsAb	Negative	Negative	Negative	Negative	Positive/Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA IU/mL#	Often > 10^7	10^4–10^7	Often < 2,000; sometimes > 2,000	10^3–10^7	Negative or Trace amount
ALT	Normal	Elevated or Fluctuating	Normal	Often fluctuating	Normal
Phase	Mostly in young patients, but could extend into the fourth or fifth decades	Young patients to fifth Decade with active hepatitis	Variable duration with HBV immune control	Mostly in older patients with intermittent flare of hepatitis	Immune clearance of HBV or immune control of the virus with occult hepatitis B
Non-invasive fibrosis assessment or biopsy	Normal (recent data arguing may be at higher risk HCC)	Abnormal	Normal or mildly abnormal	Abnormal	Normal
Treatment	No	Yes (if no signs of spontaneous seroconversion as prolonged duration of hepatitis increases fibrosis risk)	No	Yes	No (except during immune-suppression)

All patients should be fully evaluated including history, physical exam, liver tests etc., to determine need for treatment. #1 IU/mL = ~ 5 virus copies/mL

long-term NA, qHBsAg levels < 100 IU/mL are associated with a low risk of relapse (38). HBV genome analysis provides information on the genotype and mutations associated with drug resistance, immune escape and HBeAg negative CHB (39). HBV genotyping and specialized mutation analysis may be indicated in special clinical situations.

HBV Treatment

The objective of CHB treatment is to prevent the development of cirrhosis, liver failure and HCC but the challenge is to identify those who are at risk for the development of end-stage liver disease. Factors associated with risk of adverse outcomes include HBV DNA, age, liver fibrosis, ALT, and genotype (40,41). Long-term studies have correlated HBV DNA at

recruitment with outcome and shown that the risk of liver disease increases with higher HBV DNA (28). However, these studies included a small number of patients under age 30 and most were HBeAg negative, thus HBV DNA is a good predictor of risk of adverse outcomes mainly in HBeAg negative patients older than 30 years. Other studies have shown a correlation, between ALT and outcome (albeit a weaker association) (42). In study of > 3,000 untreated Asian patients, those with normal ALT had the lowest risk of HBV complications (43). However, the upper limit of normal (ULN) for ALT used in many labs may be too high for Asians with CHB. Therefore, expert societies now endorse ULN for males and females with CHB to be 35 and 25 U/L, respectively (20,21). Patients with normal or near normal ALT may still

harbour significant liver disease and warrant treatment. To inform treatment decisions, there should be other indicators which could include noninvasive fibrosis markers such as transient elastography (TE or FibroScan®) or serum based fibrosis markers (i.e., FibroTest®), ultrasound, or liver biopsy showing moderate fibrosis and/or inflammation. TE > 10 kPa has been correlated with cirrhosis in HBV patients and FibroTest® > 0.8 is thought be a marker of advanced fibrosis (44,45). Although liver injury is uncommon if the HBV DNA is < 2,000 IU/mL, in some a liver biopsy may be needed to confirm viral-induced liver injury. HBeAg negative CHB is associated with more advanced liver disease, and never completely remits spontaneously, thus treatment may be necessary. Young adults who are HBeAg positive usually have very high viral loads (> 7 log10 IU/mL) , yet often have no or minimal liver disease, and immediate treatment may not be necessary, even with elevated / fluctuating ALT (46), although this is questioned by recent studies (18). Overall treatment decisions should be based on age, HBV DNA, HBeAg status, and evidence of liver disease (ALT elevation, fibrosis or inflammation on biopsy or noninvasive assessment) (Figure 1).

Antiviral agents licensed to treat hepatitis B include lamivudine (LAM), adefovir (ADV), telbivudine (TBV), entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) and pegylated interferon alpha (Peg-IFN) (Table 4) (47).

Table 4: Seroconversion rates with hepatitis B antiviral therapy. A: HBeAg seroconversion rates. B: HBsAg seroconversion rates by the end of follow-up. (The duration of follow-up was not the same in all studies)

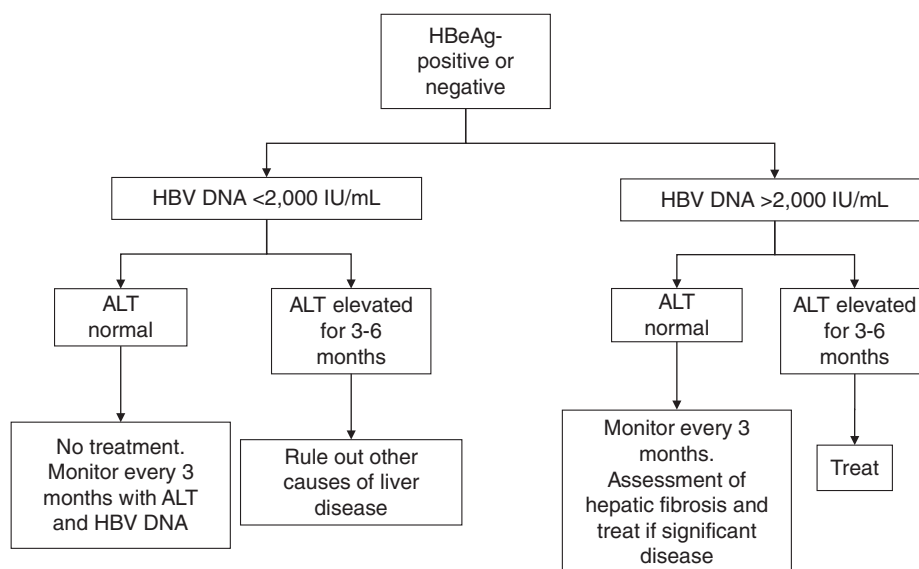|	Duration of treatment	HBeAg seroconversion rate
Pegylated interferon	24–48 weeks	29–32%
Lamivudine	1 year	17–20%
	3 years	40%
Adefovir	1 year	12%
	3 years	43%
Entecavir	1 year	21%
	3 years	39%
Telbivudine	1 year	22%
	2 years	33%
Tenofovir Disoproxil Fumarate (TDF)	1 year	21%
	7 years	40%
Tenofovir Alafenamide (TAF)	1 year	10%
	2 years	18%

Figure 1: Proposed clinical algorithm for selecting HBV patients for antiviral therapy. In general patients at risk for liver disease and needing therapy have persistently elevated ALT (normal < 25 U/L in females, < 35 U/L in males), and elevated HBV DNA. However normal ALT may not rule out liver disease risk and can fluctuate over time. Due to increased HCC risk with age, some experts are suggesting treating older patients (> age 35 or 40 years) with ongoing viremia regardless of ALT levels or fibrosis status.

LAM, ADV and TBV are second-line, and although combination therapy may be appropriate in some, there is little data to support routine use. HBV antiviral resistance is a minor issue if using first-line NA with a high barrier to resistance (TDF, TAF and ETV). Patients treated with NA should be monitored for viral breakthrough, decline in renal function and metabolic bone disease. There is conflicting data on the durability of NA response even despite consolidation therapy in HBeAg positive patients who have HBeAg seroconversion (48,49), and > 50% HBeAg negative patients relapse after discontinuation of NA therapy even after many years. Thus, all patients who discontinue NA should be monitored to rule out post-treatment relapse. Periodic TE or other noninvasive fibrosis tests and HCC screening should be done. There is evolving data on qHBsAg testing to guide NA treatment and qHBsAg is a robust predictor of response to Peg-IFN therapy (37).

IFN (Peg-IFN) have antiviral and immunomodulatory properties and can induce long-term immunological control. Advantages of IFN versus NA therapy include finite duration and no resistance, but disadvantages are the systemic side effects and subcutaneous injection. IFN is contraindicated in decompensated cirrhosis, but may be considered in patients with preserved hepatic synthetic function without portal hypertension. Peg-IFN for 48 weeks can be considered in HBeAg positive, and as well as carefully selected HBeAg negative patients. Details on Peg-IFN treatment administration, selection, monitoring, and early stopping rules based on qHBsAg levels is provided in the full guidelines document. An online calculator is available to predict treatment response in HBeAg+ patients (50) (www.liver-GI.nl/peg-ifn).

Tenofovir disoproxil fumarate (TDF) is an oral nucleotide reverse transcriptase inhibitor. TDF is effective in treatment-naïve HBeAg positive and HBeAg negative CHB. Phase 3 studies (51) reported HBV DNA suppression and normalization of ALT in most, and HBeAg loss in 59% of HBeAg positive patients and HBsAg loss in 12% of patients after 7 years. At the end of 5 years, 80% had improvement in liver histology, including patients with cirrhosis at baseline (52). Nephrotoxicity and hypophosphatemia with long term therapy were uncommonly reported. No confirmed cases (i.e., based on in vitro testing) of TDF antiviral resistance was documented after 8 years of treatment (53). Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir. TAF is given at a lower dose but is delivered more efficiently into hepatocytes. In phase 3 studies, TAF was compared with TDF for 2–3 years, followed by 5 years of open-label TAF (54,55). Although virologic and serologic responses were similar, higher rates of ALT normalization were seen in those on TAF. Moreover, eGFR as well as bone mineral density changes were less common in the TAF treated group. Although TAF has not been studied in antiviral-resistant patients, a small number in the registration studies had LAM, ADV and ETV-resistant mutations at baseline, and response to TAF was similar. Based on in vitro studies and case reports, TAF is expected to be active against antiviral-resistant HBV (56). Entecavir (ETV) is a selective guanosine analogue and a potent inhibitor of HBV replication that is well tolerated. In treatment naïve patients, HBeAg seroconversion is similar to other oral NA, ETV-treated patients had higher rates of HBV DNA suppression and histologic improvement compared with LAM (57). Only 1–2% of treatment naïve subjects developed ETV resistance after 5 years (58) compared with > 50% resistance in those with prior LAM resistance (59). In HBeAg negative patients, virologic suppression and histologic improvement were significantly higher compared with LAM. In a real-world study after 7 years of ETV, 99% maintained HBV DNA suppression, 98% normalized ALT, 82% achieved HBeAg seroconversion, and resistance was reported in 1.2% of patients (60). In a study of LAM-refractory patients treated with high dose ETV (1 mg daily), only 20% achieved undetectable HBV DNA, and 8% developed ETV resistance which increased with duration of therapy (61). ETV is not recommended for LAM-resistant HBV (Figures 2–3).
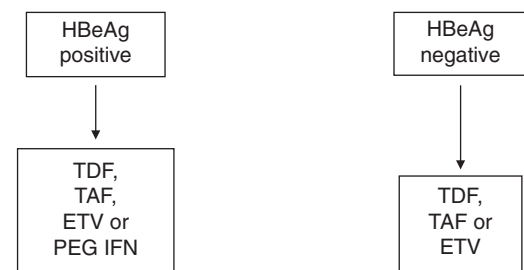

Figure 2: Algorithm for selection of specific agents for hepatitis B. The recommended first line oral nucleos(t)ide analogue therapy is tenofovir disproxil fumarate (TDF), tenofovir alafenamide (TAF), or entecavir (ETV) if patients have no pre-existing resistance to lamivudine. TAF or ETV may be considered in selected populations that have or are at risk for renal disease or metabolic bone disease. Some HBeAg positive patients (high ALT, Genotype A or B, lower HBV DNA levels) may respond to finite therapy with pegylated-interferon (Peg-IFN).
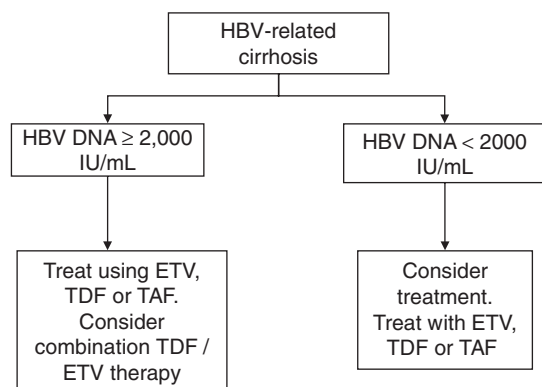
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                    ┌─────────────────┐
                    │   HBV-related   │
                    │    cirrhosis    │
                    └─────────────────┘
              ┌───────────┴───────────┐
      ┌───────────────┐       ┌───────────────┐
      │ HBV DNA ≥ 2,000│       │ HBV DNA < 2000 │
      │    IU/mL       │       │    IU/mL       │
      └───────────────┘       └───────────────┘
              │                       │
      ┌───────────────┐       ┌───────────────┐
      │ Treat using ETV,│      │   Consider    │
      │  TDF or TAF.   │       │  treatment.   │
      │   Consider     │       │ Treat with ETV,│
      │ combination TDF/│      │  TDF or TAF   │
      │  ETV therapy   │       │               │
      └───────────────┘       └───────────────┘
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Figure 3: Suggested algorithm for management of patients with hepatitis B viral cirrhosis. Cirrhotic patients are at high risk of hepatic decompensation with virological and biochemical (hepatic) flares and progression to HCC. Thus, potent nucleos(t)ide analogue therapy is recommended with Tenofovir (TDF) or Entecavir (ETV, if no history of lamivudine resistance). Some studies indicate that initiating combination therapy is beneficial in rapidly suppressing viral load in patients with cirrhosis.

Management of HBV and Pregnancy and Prevention of Mother-to-Child Transmission

All Canadian health care jurisdictions mandate prenatal HBsAg screening (13). Decisions on antiviral therapy in women of childbearing age or in early pregnancy should consider the severity of HBV-related liver disease and the antiviral safety. Peg-IFN is contraindicated in pregnancy, thus pregnant women and those of childbearing age who require immediate treatment should be initiated on a NA that is safe in pregnancy. Women who become pregnant while already on therapy, should continue treatment with a drug safe in pregnancy. Studies in pregnant women using LAM, TBV or TDF demonstrate no evidence of harm to the fetus (62–64) including data in the Antiretroviral Pregnancy Registry (65). TDF is the preferred NA due to lack of resistance, LAM and TBV may be used if TDF is contraindicated.

Administration of hepatitis B immunoglobulin (HBIG) and HBV vaccine within 12 hours of birth followed by second and third vaccine doses at 1 and 6 months in infants born to HBsAg positive women has been shown to decrease the risk of mother to child transmission (MTCT) from > 90% to ~10%. The primary risk factor for immunoprophylaxis failure is high HBV DNA levels (66). LAM, TBV and TDF have been shown to further decrease MTCT risk (62–64). In a randomized controlled trial of TDF vs. placebo in mothers with HBV DNA > 200,000 IU/mL (with immunoprophylaxis administered to all infants) (64), MTCT occurred in 7% of placebo vs. none in the TDF group. In contrast, a second double blind clinical trial of 331 women with median HBV DNA 1.0×10^8 IU/mL randomized to placebo (N = 163) vs. TDF (N = 168) at 28 weeks of gestation, showed that 2% of infants in placebo group were infected compared with 0% in TDF group, with no statistical significance between groups. However, in the second study, it was noted that all infants received very early immunoprophylaxis (within 1.2–1.3 hours after birth), 5 doses of the HBV vaccine and TDF treatment was started earlier (at 28 vs 30–32 weeks) (67). Given this robust data on efficacy, safety and resistance profile, TDF is recommended for prevention of HBV MTCT. Therapy should be initiated at 24–32 (~28) weeks of gestation, or earlier initiation in those with risk factors for pre-term labour, pregnancy with multiples, and women undergoing invasive procedures, such as amniocentesis, or in women with a viral load greater > 9 log10 IU/mL. The optimal duration of NA therapy post-partum (if given to prevent MTCT) is uncertain, prolonging therapy 4–12 weeks postpartum decreases the likelihood of ALT flares, however these are generally mild and self-limited (68). Breastfeeding is not contraindicated. TDF is excreted in breastmilk but at low concentrations (69) and HBV is detectable in breast milk but does not increase risk (70). As Cesarean section does not further decrease the risk of MTCT, it is not recommended outside of obstetrical indications (71). As prevention strategies cannot eliminate risk, babies should be tested for anti-HBs and HBsAg at 1–4 months after the last vaccine dose to confirm immunity (13). Although the incidence of vaccine escape mutations is rare, there are case reports and if indicated, repeat testing at an older age (66).

HBV Infected Health-Care Providers

All susceptible HCWs should be vaccinated for HBV (13). Since the introduction of HBV screening in the 1970's, there have been ~400 HCW to patient transmission (72). Synthesis of the data suggest that HCWs not involved in exposure-prone procedures (EPPs) do not transmit HBV unless there is a breach in Infection Prevention Control (IPC) practices (72,73). Defining EPPs remains challenging due to varying surgical techniques and individual patterns of practice, but

EPP's are defined as procedures that occur in areas difficult to access and risk of puncture wound (74,75). The Centers for Disease control (CDC) categorize only a limited number of EPP as Category I (increased risk for the transmission of HBV from HCW to patient (73)). Although the lowest HBV DNA documented in a surgeon transmitting HBV to a patient is 4×10^4 virus copies / ml (6.9×10^3 IU/ml), viral load cut-offs of 200–2,000 IU/ml have been recommended in Europe (20,72) and in the United States (73,74). The PHAC has set a threshold of 1,000 IU/ml (or 2,000 IU/mL in the province of Quebec (76)). Anti-HBV NA will suppress HBV DNA in most, and is recommended in HCWs who engage in EPPs. As a level of 1,000 IU/ml does not align with indications for therapy, the pros and cons of initiating NA should be discussed. All HCWs with CHB should be under the care of a physician with expertise in HBV management and understand IPC practices to minimize the risk of transmission.

Management of Hepatitis B in Immunosuppressed Patients

Both HBsAg positive as well as HBsAg negative, anti-HBc positive individuals undergoing immunosuppressive (IS) therapy are at risk for severe HBV reactivation, which is classified as high (> 10%), moderate (1–10%) or low risk (< 1%) (77,78) (Table 5). All candidates for IS should be screened for HBsAg, anti-HBc and anti-HBs, those who are non-immune should be vaccinated (13). In those at lower risk for reactivation, monitoring is recommended, whereas those at higher risk, should receive prophylactic NA therapy. Although the use of LAM in this setting has been extensively studied (79), recent studies have shown potent NA's such as ETV are superior in the prevention of reactivation in those at high risk (80). The risk of HBV reactivation continues after IS completion, thus NA therapy should continue for at least 6–12 months and even longer in those undergoing potent IS with B-cell depleting therapy (up to 2 years)

Table 5: Risk of HBV reactivation with immunosuppression/chemotherapy in HBsAg positive and HBsAg negative, anti-HBc positive patients

Risk group	HBV serology	Immunosuppressive/chemotherapy
High-risk group (> 10%)	HBsAg positive OR HBsAg negative/anti-HBc positive (high risk regardless of anti-HBs titre levels)	• B cell-depleting agents such as rituximab and ofatumumab
	HBsAg positive	• Anthracycline derivatives such as doxorubicin and epirubicin • Corticosteroid therapy for ≥ 4 wk (prednisone equivalent > 10–20 mg/day)
Moderate-risk group (1%–10%)	HBsAg positive OR HBsAg negative/anti-HBc positive (may be lower risk and monitoring sufficient if high anti-HBs titres > 100 IU/L)	• TNF-α inhibitors: etanercept, adalimumab, certolizumab, certolizumab, infliximab • Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab • Tyrosine kinase inhibitors: imatinib, nilotinib, ibrutinib
	HBsAg positive	• Corticosteroid therapy for ≥ 4 wk (prednisone equivalent < 10 mg/day)
	HBsAg negative/anti-HBc positive (may be lower risk and monitoring sufficient if high anti-HBs titres > 100 IU/L)	• Corticosteroid therapy for ≥ 4 wk (prednisone equivalent > 10–20 mg/day) • Anthracycline derivatives: doxorubicin and epirubicin
Low-risk group (< 1%)	HBsAg positive OR HBsAg negative/anti-HBc positive (low risk especially if high anti-HBs titres > 100 IU/L)	• Traditional immunosuppressive agents: azathioprine, 6-mercaptopurine, methotrexate • Intra-articular corticosteroids • Corticosteroid therapy for ≤ 1 wk
	HBsAg negative/anti-HBc positive (low risk especially if high anti-HBs titres > 100 IU/L)	• Corticosteroid therapy for ≥ 4 wk (prednisone equivalent < 10 mg/day)

(81). With development of novel immune modulating therapy, the risk of HBV reactivation is unclear at the time of introduction into clinical use, hence monitoring ALT and HBV DNA is recommended (Figure 4).

HBV Associated Renal Disease and Management of Hepatitis B in Patients with End-Stage Renal Disease

Extrahepatic manifestations of HBV may occur in CHB through circulating immune complexes deposition and complement activation. A kidney biopsy demonstrating HBV antigen deposition is required for diagnosis (82). Renal extrahepatic manifestations include membranoproliferative glomerulonephritis (MPGN), membranous nephropathy (MN), polyarteritis nodosa, IgA nephropathy, mesangial proliferative glomerulonephritis, and amyloidosis (83). In HBV associated glomerulonephritis (GN), circulating immune complexes deposition in the renal glomeruli can cause severe destruction of the glomeruli. In children, GN is usually self-limited but in adults, HBV induced GN can progress to renal failure. An immune complex serum-sickness like syndrome can cause self-limiting arthritis and dermatitis, and cryoglobulinemia has been reported in association with CHB. Treatment is recommended with potent NA that have lower nephrotoxicity (i.e., ETV or TAF).
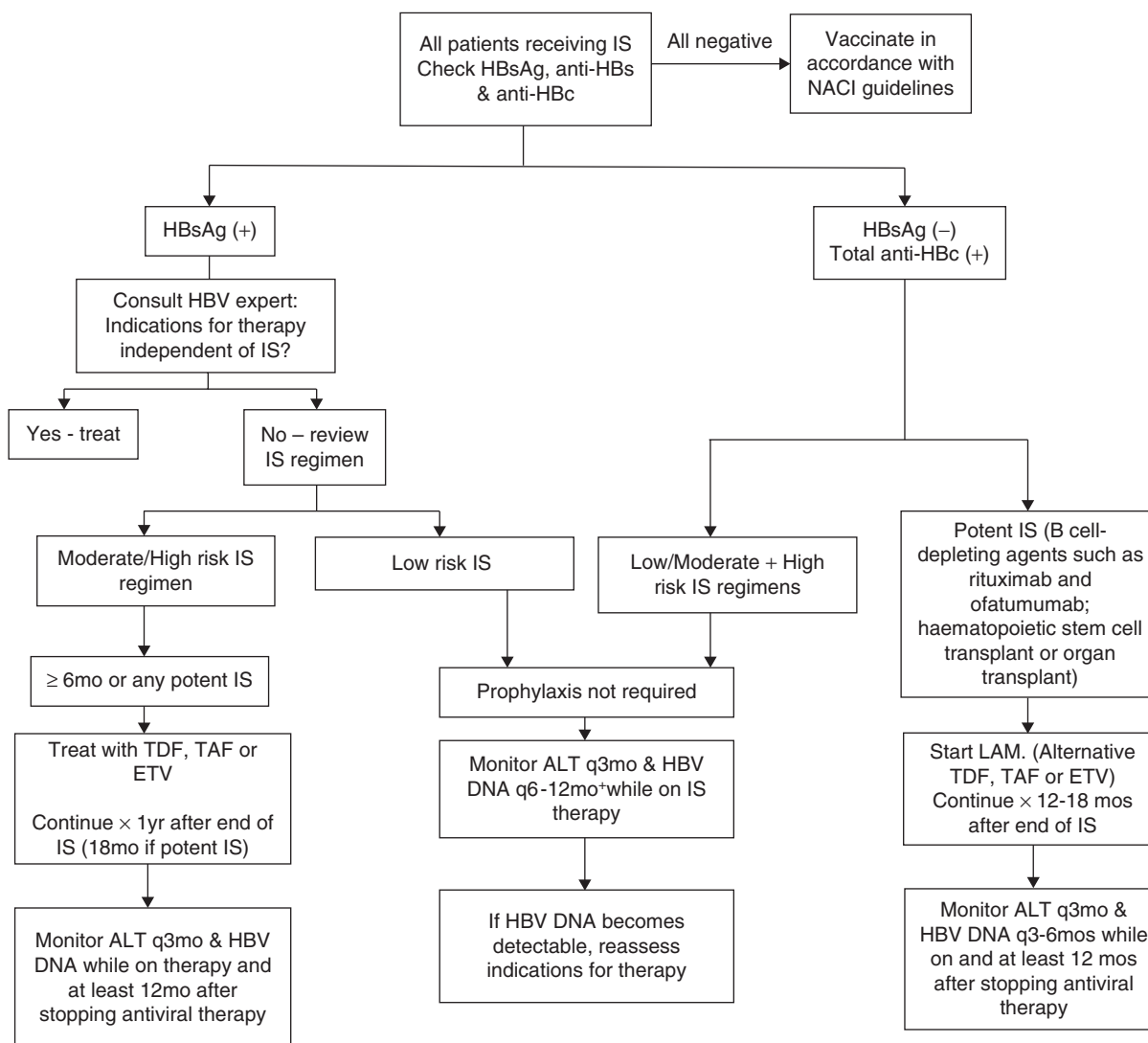

Figure 4: Algorithm for Management of hepatitis B in Immuno-suppressed patients. All patients should be screened for HBV and offered vaccination if at risk. HBsAg positive patients should receive prophylaxis with most regimens. HBsAg negative, anti-HBc positive patients with immunosuppression may be treated with first generation NA (LAM) due to lower risk of resistance in those with undetectable HBV DNA.

All anti-HBV NA undergo renal clearance and have been shown to impact renal function in some patients due to alteration in tubular transport, and mitochondrial injury. Cases of severe tubular damage leading to Fanconi syndrome have been described with TDF, especially in HBV-HIV coinfection (84,85), with reports of eGFR improvement after switch to ETV. Although eGFR declines are more common with TDF, other NA have also shown a risk for renal injury (86). In patients with chronic kidney disease, options include TDF, ETV or TAF. TDF and ETV require dose adjustment for eGFR < 50 ml/min, while TAF does not require dose adjustment if eGFR ≥ 15 ml/min. TAF was shown to be superior to TDF in preservation of renal function and less progression to chronic kidney disease (54,55,87). There are also data showing reduced proteinuria, albuminuria and tubular protein losses in HIV-HBV coinfected individuals on TAF (88). We recommend either ETV or TAF as first line if eGFR is less than < 60ml/min, with preference to TAF among patients with prior exposure and/or resistance to LAM. In dialysis patients or eGFR < 15 ml/min, treatment options include renally-dosed ETV or TDF.

Management of Hepatitis B and Decompensated Cirrhosis

It is estimated that patients with HBV-related cirrhosis will progress to decompensated cirrhosis at a rate of 3% annually. The 5-year survival rate is 84% in patients with compensated cirrhosis, but only 14%–35% in decompensated cirrhosis (89). In a cirrhotic patient, decompensated cirrhosis is defined by new onset episode of jaundice, or by the presence of ascites, hepatic encephalopathy or variceal bleeding. In patients with advanced cirrhosis, risk factors for short-term mortality are hepatic dysfunction (low serum albumin, low platelets, increased serum bilirubin), the presence of ascites or hepatic encephalopathy, advanced age, and portal hypertension (90). Patients with decompensated cirrhosis should be referred for liver transplantation (LT) and treated with NAs. High Child-Pugh or Model for End-Stage Liver Disease (MELD) scores are predictors of poor survival. In patients with decompensated cirrhosis, NA must be started as soon as possible and continue lifelong (91,92). Peg-IFN is contraindicated in patients with severe liver disease, ETV or TDF are preferred in view of their potency and low rates of drug resistance. There are a few reports in patients with decompensated

liver disease of NA induced lactic acidosis by inhibiting mitochondrial polymerase γ in liver and muscle (93). Because of its favourable safety profile with regards to kidney function, TAF could be an option in patients with decompensated cirrhosis, but safety data is lacking. NA treatment leads to clinical improvement in 40–50% with decompensated HBV cirrhosis and approximately one third of them can be delisted for transplant (91).

Management of Hepatitis B in Liver Transplantation

Due to the efficacy of NAs, HBV-related severe liver disease has become an uncommon indication for LT, other than HBV-related HCC. Recurrent HBV infection after transplant was a major problem, but it is now very rare with the usage of HBIG and NA which prevents reinfection of the graft in > 95% of cases (94). All HBV patients considered for LT should be treated with NAs in order to achieve undetectable HBV-DNA levels pre-transplant. ETV or TDF are recommended with TDF preferred for patients with prior LAM resistance (95). ETV is preferable in patients with post-LT renal impairment (96). There is variation in transplant centre practise regarding HBIG usage, generally sub-cutaneous or intra-muscular HBIG is used (97), and can be discontinued at 6–12 months with NA monotherapy in selected patients with a low risk of HBV recurrence (98). HBsAg-negative LT recipients receiving a liver from a donor with evidence of past HBV infection (HBsAg-negative and anti-HBc-positive) are at risk of HBV reactivation due to IS and should receive NA prophylaxis, LAM is a reasonable choice especially if high anti-HBs titres (99).

Management of Acute Hepatitis B Infection

Antiviral therapy is usually not necessary in acute hepatitis B, as 90–95% of immunocompetent adults will recover spontaneously. Severe or fulminant acute hepatitis B is rare but life-threatening. Severe acute hepatitis B is defined by the presence of coagulopathy (INR> 1.5) or marked jaundice for > 4 weeks, and fulminant hepatitis by the presence of hepatic encephalopathy. Two small randomized controlled trials of LAM vs. placebo in patients with severe acute hepatitis B found no difference in clinical outcomes (100,101). Despite the lack of strong evidence, NA therapy is recommended in all patients with severe acute hepatitis B who are candidates for LT to reduce the risk of recurrent hepatitis B after transplant (20,21).

Management of HBV and Human Immunodeficiency Virus Co-Infection

All people living with HIV should be screened for HBV infection, and if non-immune, should receive the HBV vaccine (6). Co-infection is associated with more rapid liver fibrosis progression, cirrhosis and risk of HCC (102). TDF, TAF, and LMV are active against both HIV and HBV, and should be included in HIV antiretroviral regimens, irrespective of CD4+ T cell count. Monitoring for HBV-specific immune reconstitution for 3 months after treatment initiation is recommended (102). There is a risk for proximal tubular nephropathy and osteopenia, especially with TDF. Emerging data suggests anti-HIV and HBV efficacy as well as safety in HIV-HBV co-infected TAF recipients, hence TAF may be the preferred NA (88). HIV infection is not a contraindication to LT as post-LT outcomes are comparable to HBV mono-infection (103).

Management of HBV and Hepatitis C Virus (HCV) Coinfection

Due to shared risk factors, HBV and HCV can be found concurrently and screening for both is recommended. In HBV/HCV co-infection, fibrosis progression and HCC risk is increased (104). There is a risk of HBV flare in HBsAg positive individuals initiating HCV DAA therapy. Based on suboptimal data, this risk appears to be low but can result in fulminant hepatitis (105). Co-initiation of a HBV antiviral with DAA dosing should be considered with HBV NA therapy maintained for 12 weeks following anti-HCV DAA completion (106). An acceptable alternative is to monitor without initiation of HBV antiviral. Irrespective of whether a HBV antiviral is initiated, liver enzymes and HBV DNA levels should be monitored while on DAA therapy up to 24 weeks following completion (20). ALT monitoring is advised for HBsAg negative / anti-HBc positive individuals, especially if cirrhotic. The incidence of HBV flares with DAA treatment is uncommon (< 10% low-level HBV viremia) in the anti-HBc positive population (105)

Management of HBV-Hepatitis Delta Virus (HDV) Coinfection

The HDV relies on HBsAg for viral entry (107), and is spread by similar blood-borne or sexual transmission routes, either simultaneously or as a superinfection. Approximately 15 million people worldwide have HDV coinfection (108). In the US and Europe ~8% of HBV carriers have HDV co-infection, especially in PWID (109). The screening test is HDV antibody and HDV RNA to confirm active infection (109). Compared with HBV mono-infection, co-infected individuals are more likely to develop end-stage liver disease (108). Non-invasive assessment of fibrosis and other scores are not well validated in HDV/HBV patients, hence liver biopsy is needed to stage disease (110). The anti-HBV NA are not effective, Peg-IFN is the only approved therapy (111) but is effective in ~20–30% (112) and late relapse is often observed (113). Long-term follow-up of Peg-IFN treated patients show lower likelihood for liver disease progression (114). A clinical score has been developed to predict patients that are at increased risk of liver related complications, and should be considered for IFN treatment (115). There is a reported risk of HBV reactivation with suppression of HDV, hence monitoring for HBV flares is recommended during Peg-IFN therapy, and consider NA to block residual HBV replication especially in those with cirrhosis. HDV/HBV co-infected patients with cirrhosis should undergo HCC surveillance.

Management of Hepatitis B in Pediatric Patients

There is limited recent Canadian data on HBV prevalence in pediatrics. In 2009, Statistics Canada reported a prevalence of ~0.4% in 14–49 age group, thus including some adolescents, especially in non-Caucasian, foreign-born children. A recent report from an Ontario pediatric centre noted that 85% of HBV infected children was Asian (116). In a Quebec series, ~43% were Asian (mostly adopted from Asia) (117). The majority of children are asymptomatic at presentation but rarely may present with acute liver failure. Asian children (infected by vertical transmission) show delayed HBeAg seroconversion, compared with those infected horizontally. HBeAg seroconversion occurs < 10 years for the latter, and in puberty (118) for those infected vertically (117). Factors predicting HBeAg seroconversion include increased ALT, HBV DNA decrease (119) and, inflammatory activity on liver biopsy. Overall, the presence of severe hepatitis or fibrosis are infrequent in children with CHB. Treated children show a tendency to undergo HBeAg seroconversion faster than untreated patients, however, by age 18 the difference is not significant. Approximately 20% show spontaneous HBsAg / anti-HBs seroconversion by age 18, mainly in children infected horizontally that have already shown

HBeAg seroconversion (120). Extrahepatic complications are rare (< 1%), and usually require treatment. HDV co-infection is rare and associated with more rapid fibrosis progression (121). Cirrhosis occurs in 3% of infected children, usually at young age, with increased risk for HCC, although HBeAg and HBsAg seroconversion leads to fibrosis regression. HBeAg negative hepatitis is observed in ~5% of children especially in children of Mediterranean descent with HBV genotype D infection (122).

Children with normal ALT and low level HBV DNA usually have a favourable long-term outcome (122). Although the available therapies can induce HBeAg seroconversion ~ 3 years earlier than spontaneous seroconversion (46,117,122–125), the long-term benefits of this shorter window remain unknown. Accordingly, the decision to treat HBV should account for the presence and degree of persistent inflammation associated with high HBV DNA levels balanced with the cost and limited long-term data on exposure to treatment. Data predominantly based on studies in Asia suggest earlier treatment should be considered even in young persons with normal liver enzymes (18,126). At present, non-invasive evaluation of the liver by TE has not been validated, hence liver biopsy may be needed to accurately stage liver disease in children. In general treatment indications and monitoring in pediatrics are similar to adults (i.e., elevated ALT, HBV DNA > 2,000 IU/L, severe liver inflammation and fibrosis, cirrhosis, extrahepatic disease). A detailed discussion of all treatment options and dosing is provided in the online full guidelines (https://canlivj.utpjournals). ETV and TDF are first line therapy. ETV has been used > 2 years of age (dose of 0.015 mg/kg, maximum of 0.5 mg/day) in children < 32.5 kg and 0.5 mg/day in those > 32.6 kg for > 1 year. HBeAg seroconversion and HBV DNA < 50 IU/mL was 24.2% vs. 3.3% in placebo at week 48 (p< 0.0008). Emergent resistance was 2.6% at the end of 2nd year of treatment (127). TDF has been used > 12 years old at dose of 300 mg daily > 1 year. After 42 weeks, HBeAg seroconversion was 21% vs 15% (ns) in the placebo group. No adverse event was recorded; however, monitoring of renal function is suggested (128).

Conclusion

Hepatitis B leads to significant morbidity and mortality in many Canadians. All provinces and territories should offer universal infant / neonatal vaccination. There should be systematic programs for screening of high risk groups and linkage of individuals to care. Advances in HBV virological / serological diagnostic tests, non-invasive tests for assessment of liver disease and antiviral therapy has led to improved prognosis for many patients diagnosed with hepatitis B. Current treatment does not offer a virological or a functional cure for hepatitis B and there are new therapies in development for CHB. These guidelines summarize current best practice management but also to highlight the need for increased resources for treatment and research on hepatitis B pathogenesis and epidemiology in Canada.

LIST OF ABBREVIATIONS

ADV	– Adefovir
AFP	– Alpha-fetoprotein
ALT	– alanine aminotransferase
AMMI	– Association of Medical Microbiology and Infectious Disease Canada
AGREE-II	– Appraisal of Guidelines for Research & Evaluation
Anti-HBs	– Antibody to HBsAg
Anti-HBc	– Antibody to HBV core
Anti-HBe	– Antibody to HBeAg
CASL	– Canadian Association for the Study of the Liver
CNDSS	– Canadian Notifiable Disease Surveillance System
CHB	– Chronic Hepatitis B
CDC	– Centers for Disease Control
DAA	– Directly Acting Antiviral Therapy
EPP	– Exposure Prone Procedures
ETV	– Entecavir
eGFR	– Estimated Glomerular Filtration Rate
GRADE	– Grades of Recommendation, Assessment Development and Evaluation
GN	– Glomerulonephritis
HBV	– Hepatitis B Virus
HBV cccDNA	– HBV covalently closed circular DNA
HBcrAg	– HBV Core Related Antigen
HBIg	– Hepatitis B Immune Globin
HBsAg	– Hepatitis B Surface Antigen
HBeAg	– HBV E antigen

HCC	– Hepatocellular Carcinoma
HCW	– Health Care Workers
HCV	– Hepatitis C Virus
HDV	– Hepatitis Delta Virus
HIV	– Human Immunodeficiency Virus
IS	– Immunosuppressive Therapy
IU / mL	– International Units / millilitre
IFN or (PEG-IFN)	– Interferon or Pegylated Interferon alpha
IPC	– Infection Prevention and Control
LAM	– Lamivudine
MELD	– Model for End-Stage Liver Disease
MPGN	– Membranoproliferative Glomerulonephritis
MSM	– Men Who Have Sex with Men
MTCT	– Mother to Child Transmission
NA	– Nucleos(t)ide Analogues
NTCP	– Sodium Taurocholate Cotransporting Polypeptide
PAN	– Polyarteritis Nodosa
PrEP	– Pre-Exposure Prophylaxis
PWID	– Persons Who Inject Drugs
pgRNA	– HBV pregenomic RNA
qHBsAg	– Quantitative Hepatitis B Surface Antigen
OHB	– Occult Hepatitis B
TBV	– Telbivudine
TAF	– Tenofovir Alafenamide
TDF	– Tenofovir Disoproxil Fumarate
TE	– Transient Elastography
TLR	– Toll Like Receptor
YMDD	– tyrosine-methionine-aspartate-aspartate

REFERENCES

1. Sherman M, Bain V, Villeneuve JP, et al. The management of chronic viral hepatitis: a Canadian consensus conference 2004. Canadian Journal of Gastroenterology 2004;18(12): 715–28. https://doi.org/10.1155/2004/201031. Medline: 15605136

2. Coffin CS, Fung SK, Ma MM, et al. Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines. Can J Gastroenterol 2012;26(12):917–38. https://doi.org/10.1155/2012/506819. Medline: 23248795

3. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 2010;182(18):E839–42. https://doi.org/10.1503/cmaj.090449. Medline: 20603348

4. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924–6. https://doi.org/10.1136/bmj.39489.470347.AD. Medline: 18436948

5. Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015;386(10003):1546–55. https://doi.org/10.1016/S0140-6736(15)61412-X.

6. World Health Organization. Hepatitis B (Fact sheet no. 204). Geneva Switzerland: Updated July 2017.

7. Public Health Agency of Canada (PHAC). Hepatitis B Infection in Canada: Brief Report. 2011.

8. Sherman, M. Canadian Liver Foundation Special Report. Liver Disease in Canada, A Crisis in the Making, 2013. www.liver.ca.

9. Wu HX, Andonov A, Giulivi A, et al. Enhanced surveillance for childhood hepatitis B virus infection in Canada, 1999–2003. Int J Med Sci 2005;2(4):143–6. https://doi.org/10.7150/ijms.2.143. Medline: 16239952

10. Zhang J, Zou S, Giulivi A. Epidemiology of hepatitis B in Canada. Can J Infect Dis 2001;12(6):345–50. https://doi.org/10.1155/2001/790915. Medline: 18159361

11. Kwong JC, Ratnasingham S, Campitelli MA, et al. The impact of infection on population health: results of the Ontario burden of infectious diseases study. PLoS One 2012;7(9):e44103. https://doi.org/10.1371/journal.pone.0044103. Medline: 22962601

12. Wong WW, Woo G, Heathcote EJ, et al. Disease burden of chronic hepatitis B among immigrants in Canada. Can J Gastroenterol 2013;27(3): 137–47. https://doi.org/10.1155/2013/924640. Medline: 23516678

13. Public Health Agency of Canada (PHAC). Canadian Immunization Guide: Hepatitis B Vaccine: http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-hepb-eng.php-a4, Accessed January 2018.

14. Public Health Agency of Canada (PHAC). Vaccine Coverage in Canadian Children, Results from the 2013 Childhood National Immunization Coverage Survey (CNICS). May 2016.

15. Rotermann M, Langlois K, Andonov A, et al. Seroprevalence of hepatitis B and C virus infections: Results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey. Health Rep 2013;24(11):3–13. Medline: 24259199

16. Lok AS, Lai CL, Wu PC, et al. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. Gastroenterology 1987;92(6):1839–43. https://doi.org/10.1016/0016-5085(87)90613-5. Medline: 3569757

17. Kennedy PTF, Sandalova E, Jo J, et al. Preserved T-cell function in children and young adults with immune-tolerant chronic hepatitis B. Gastroenterology 2012;143(3):637–45. https://doi.org/10.1053/j.gastro.2012.06.009. Medline: 22710188

18. Kennedy PTF, Litwin S, Dolman GE, et al. Immune Tolerant Chronic Hepatitis B: The Unrecognized Risks. Viruses 2017;9(5):9. https://doi.org/10.3390/v9050096.

19. Tseng TC, Liu CJ, Yang HC, et al. Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus loads. Hepatology 2013;57(2):441–50. https://doi.org/10.1002/hep.26041. Medline: 22941922

20. European Association for the Study of the Liver (EASL). 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370–98. https://doi.org/10.1016/j.jhep.2017.03.021. Medline: 28427875

21. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63(1):261–83. https://doi.org/10.1002/hep.28156. Medline: 26566064

22. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10(1):1–98. https://doi.org/10.1007/s12072-015-9675-4. Medline: 26563120

23. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009;49(S5):S45–55. https://doi.org/10.1002/hep.22898. Medline: 19399792

24. Chu CM, Liaw YF. Hepatitis B virus-related cirrhosis: natural history and treatment. Semin Liver Dis 2006;26(2):142–52. https://doi.org/10.1055/s-2006-939752. Medline: 16673292

25. Villeneuve JP, Desrochers M, Infante-Rivard C, et al. A long-term follow-up study of asymptomatic hepatitis B surface antigen-positive carriers in Montreal. Gastroenterology 1994;106(4):1000–5. https://doi.org/10.1016/0016-5085(94)90760-9. Medline: 8143967

26. Qu LS, Liu JX, Zhang HF, et al. Effect of serum hepatitis B surface antigen levels on predicting the clinical outcomes of chronic hepatitis B infection: A meta-analysis. Hepatol Res 2014;45(9):1004–13. https://doi.org/10.1111/hepr.12444. Medline: 25355455

27. Liu C, Xiao GQ, Yan LN, et al. Value of alpha-fetoprotein in association with clinicopathological features of hepatocellular carcinoma. World J Gastroenterol 2013;19(11):1811–9. https://doi.org/10.3748/wjg.v19.i11.1811. Medline: 23555170

28. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. Jama 2006;295(1):65–73. https://doi.org/10.1001/jama.295.1.65. Medline: 16391218

29. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011;12(6):568–74. https://doi.org/10.1016/S0140-6736(11)61290-7.

30. Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64(4):800–6. https://doi.org/10.1016/j.jhep.2015.11.035. Medline: 26678008

31. Sharma SA, Kowgier M, Hansen BE, et al. Toronto HCC risk index: A validated scoring system to predict 10-year risk of HCC in patients with cirrhosis. J Hepatol 2017;68(1). Aug 24. https://doi.org/10.1016/j.jhep.2017.07.033. Medline: 28844936

32. Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology 2016;150(4):835–53. https://doi.org/10.1053/j.gastro.2015.12.041. Medline: 26795574

33. Kumar R, Perez-Del-Pulgar S, Testoni B, et al. Clinical relevance of the study of hepatitis B virus covalently closed circular DNA. Liver Int 2016;36 Suppl 1:72–7. https://doi.org/10.1111/liv.13001. Medline: 26725901

34. Makvandi M. Update on occult hepatitis B virus infection. World J Gastroenterol 2016;22(39):8720–34. https://doi.org/10.3748/wjg.v22.i39.8720. Medline: 27818588

35. Marcellin P, Martinot-Peignoux M, Asselah T, et al. Serum Levels of Hepatitis B Surface Antigen Predict Severity of Fibrosis in Patients With E Antigen-Positive Chronic Hepatitis B. Clin Gastroenterol Hepatol 2015;13(8):1532–9 e1. https://doi.org/10.1016/j.cgh.2014.12.017. Medline: 25542306

36. Brouwer WP, Chan HL, Brunetto MR, et al. Repeated Measurements of Hepatitis B Surface Antigen Identify Carriers of Inactive HBV During Long-term Follow-up. Clin Gastroenterol Hepatol 2016;14(10):1481–9 e5. https://doi.org/10.1016/j.cgh.2016.01.019. Medline: 26872398

37. Peng H, Wei F, Liu JY, et al. Response-guided therapy of regimens based on PEG-interferon for chronic hepatitis B using on-treatment hepatitis B surface antigen quantification: a meta-analysis. Hepatol Int 2015;9(4):543–57. https://doi.org/10.1007/s12072-015-9644-y. Medline: 26162453

38. Hsu YC, Mo LR, Chang CY, et al. Association Between Serum Level of Hepatitis B Surface Antigen at End of Entecavir Therapy and Risk of Relapse in E Antigen-Negative Patients. Clin Gastroenterol Hepatol 2016;14(10):1490–8 e3. https://doi.org/10.1016/j.cgh.2016.03.024. Medline: 27018299

39. Lin CL, Kao JH. Hepatitis B virus genotypes and variants. Cold Spring Harb Perspect Med 2015;5:a021436. https://doi.org/10.1101/cshperspect.a021436. Medline: 25934462

40. Chen G, Lin W, Shen F, et al. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. Am J Gastroenterol 2006;101(8):1797–803. https://doi.org/10.1111/j.1572-0241.2006.00647.x. Medline: 16817842

41. Yu MW, Yeh SH, Chen PJ, et al. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. J Natl Cancer Inst 2005;97(4):265–72. https://doi.org/10.1093/jnci/dji043. Medline: 15713961

42. Yuen MF, Yuan HJ, Wong DK, et al. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. Gut 2005;54(11):1610–4. https://doi.org/10.1136/gut.2005.065136. Medline: 15871997

43. Kim HC, Nam CM, Jee SH, et al. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ 2004;328(7446):983. https://doi.org/10.1136/bmj.38050.593634.63. Medline: 15028636

44. Vigano M, Paggi S, Lampertico P, et al. Dual cut-off transient elastography to assess liver fibrosis in chronic hepatitis B: a cohort study with internal validation. Aliment Pharmacol Ther 2011;34(3):353–62. https://doi.org/10.1111/j.1365-2036.2011.04722.x. Medline: 21631559

45. Chon YE, Choi EH, Song KJ, et al. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta-analysis. PLoS One 2012;7(9):e44930. https://doi.org/10.1371/journal.pone.0044930. Medline: 23049764

46. Lok AS, Lai CL. A longitudinal follow-up of asymptomatic hepatitis B surface antigen-positive Chinese children. Hepatology 1988;8(5):1130–3. https://doi.org/10.1002/hep.1840080527. Medline: 3417235

47. Dienstag JL, Wei LJ, Xu D, et al. Cross-study analysis of the relative efficacies of oral antiviral therapies for chronic hepatitis B infection in nucleoside-naive patients. Clin Drug Investig 2007;27(1):35–49. https://doi.org/10.2165/00044011-200727010-00003. Medline: 17177578

48. Nagata N, Kagawa T, Hirose S, et al. Off-treatment durability of antiviral response to nucleoside analogues in patients with chronic hepatitis B. BMC Gastroenterol 2016;16(1):38.

https://doi.org/10.1186/s12876-016-0454-z. Medline: 26987437

49. Reijnders JG, Perquin MJ, Zhang N, et al. Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. Gastroenterology 2010;139(2):491–8. https://doi.org/10.1053/j.gastro.2010.03.059. Medline: 20381492

50. Buster EH, Hansen BE, Lau GK, et al. Factors that predict response of patients with hepatitis B e antigen-positive chronic hepatitis B to peginterferon-alfa. Gastroenterology 2009;137(6):2002–9. https://doi.org/10.1053/j.gastro.2009.08.061. Medline: 19737568

51. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Dig Dis Sci 2015;60(5):1457–64. https://doi.org/10.1007/s10620-014-3486-7. Medline: 25532501

52. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381(9865):468–75. https://doi.org/10.1016/S0140-6736(12)61425-1. Medline: 23234725

53. Liu Y, Corsa AC, Buti M, et al. No detectable resistance to tenofovir disoproxil fumarate in HBeAg+ and HBeAg–patients with chronic hepatitis B after 8 years of treatment. J Viral Hepat 2017;24(1):68–74. https://doi.org/10.1111/jvh.12613. Medline: 27658343

54. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg–positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016;1(3):185–95. https://doi.org/10.1016/S2468-1253(16)30024-3. Medline: 28404091

55. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg–negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016;1(3):196–206. https://doi.org/10.1016/S2468-1253(16)30107-8. Medline: 28404092

56. Grossi G, Loglio A, Facchetti F, et al. Tenofovir alafenamide as a rescue therapy in a patient with HBV-cirrhosis with a history of Fanconi syndrome and multidrug resistance. J Hepatol 2018;68(1):195–8. Sep 21. https://doi.org/10.1016/j.jhep.2017.08.020. Medline: 28870666

57. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg–positive chronic hepatitis B. N Engl J Med 2006;354(10):1001–10. https://doi.org/10.1056/NEJMoa051285. Medline: 16525137

58. Colonno RJ, Rose R, Baldick CJ, et al. Entecavir resistance is rare in nucleoside naive patients with hepatitis B. Hepatology 2006;44(6):1656–65. https://doi.org/10.1002/hep.21422. Medline: 17133475

59. Tenney DJ, Rose RE, Baldick CJ, et al. Two-year assessment of entecavir resistance in Lamivudine-refractory hepatitis B virus patients reveals different clinical outcomes depending on the resistance substitutions present. Antimicrob Agents Chemother 2007;51(3):902–11. https://doi.org/10.1128/AAC.00833-06. Medline: 17178796

60. Lam YF, Seto WK, Wong D, et al. Seven-Year Treatment Outcome of Entecavir in a Real-World Cohort: Effects on Clinical Parameters, HBsAg and HBcrAg Levels. Clin Transl Gastroenterol 2017;8(10):e125. https://doi.org/10.1038/ctg.2017.51. Medline: 29072673

61. Sherman M, Yurdaydin C, Sollano J, et al. Entecavir for treatment of lamivudine-refractory, HBeAg–positive chronic hepatitis B. Gastroenterology 2006;130(7):2039–49. https://doi.org/10.1053/j.gastro.2006.04.007. Medline: 16762627

62. Han GR, Jiang HX, Yue X, et al. Efficacy and safety of telbivudine treatment: an open-label, prospective study in pregnant women for the prevention of perinatal transmission of hepatitis B virus infection. J Viral Hepat 2015;22(9):754–62. https://doi.org/10.1111/jvh.12379. Medline: 25641421

63. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. J Viral Hepat 2009;16(2):94–103. https://doi.org/10.1111/j.1365-2893.2008.01056.x. Medline: 19175878

64. Pan CQ, Duan Z, Dai E, et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med 2016;374(24):2324–34. https://doi.org/10.1056/NEJMoa1508660. Medline: 27305192

65. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 January 2017. Registry Coordinating Centre, Wilmington, NC, 2017.

66. Singh AE, Plitt SS, Osiowy C, et al. Factors associated with vaccine failure and vertical transmission of hepatitis B among a cohort of Canadian mothers and infants. J Viral Hepat 2011;18(7):468–73. https://doi.org/10.1111/j.1365-2893.2010.01333.x. Medline: 20546502

67. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus Placebo to Prevent Perinatal Transmission of Hepatitis B. N Engl J Med 2018;378(10):911–23. https://doi.org/10.1056/NEJMoa1708131. Medline: 29514030

68. Samadi Kochaksaraei G, Castillo E, Osman M, et al. Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant patients in a low hepatitis B virus endemic region. J Viral Hepat 2016;23(1):15–22. https://doi.org/10.1111/jvh.12436. Medline: 26192022

69. Benaboud S, Pruvost A, Coffie PA, et al. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. Antimicrob Agents Chemother 2011;55(3):1315–7. https://doi.org/10.1128/AAC.00514-10. Medline: 21173182

70. Tseng RY, Lam CW, Tam J. Breastfeeding babies of HBsAg-positive mothers. Lancet 1988;332(8618):1032. https://doi.org/10.1016/S0140-6736(88)90803-3. Medline: 2902484

71. Castillo E, Murphy K, van Schalkwyk J. No. 342-Hepatitis B and Pregnancy. J Obstet Gynaecol Can 2017;39(3):181–90. https://doi.org/10.1016/j.jogc.2016.11.001. Medline: 28284515

72. Gunson RN, Shouval D, Roggendorf M, et al. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in health care workers (HCWs): guidelines for prevention of transmission of HBV and HCV from HCW to patients. J Clin Virol 2003;27(3):213–30. https://doi.org/10.1016/S1386-6532(03)00087-8. Medline: 12878084

73. Centers for Disease Control (CDC). Updated CDC recommendations for the management of hepatitis B virus-infected health-care providers and students. MMWR Recomm Rep 2012;61(RR-3):1–12. Medline: 22763928

74. Henderson DK, Dembry L, Fishman NO, et al. SHEA guideline for management of healthcare workers who are infected with hepatitis B virus, hepatitis C virus, and/or human immunodeficiency virus. Infect Control Hosp Epidemiol 2010;31(3):203–32. https://doi.org/10.1086/650298. Medline: 20088696

75. Reitsma AM, Closen ML, Cunningham M, et al. Infected physicians and invasive procedures: safe practice management. Clin Infect Dis 2005;40(11):1665–72. https://doi.org/10.1086/429821. Medline: 15889366

76. Institut National De Sante Publique Du Quebec. Recommandations concernant l'évaluation et le suivi des soignants infectés par le virus de l'hépatite B (VHB), Avril 2015.

77. Reddy KR, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148(1):215–9; quiz e16–7. https://doi.org/10.1053/j.gastro.2014.10.039. Medline: 25447850

78. Hwang JP, Somerfield MR, Alston-Johnson DE, et al. Hepatitis B Virus Screening for Patients With Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update. J Clin Oncol 2015;33(19):2212–20. https://doi.org/10.1200/JCO.2015.61.3745. Medline: 25964247

79. Loomba R, Rowley A, Wesley R, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med 2008;148(7):519–28. https://doi.org/10.7326/0003-4819-148-7-200804010-00008. Medline: 18378948

80. Huang H, Li X, Zhu J, et al. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. JAMA 2014;312(23):2521–30. https://doi.org/10.1001/jama.2014.15704. Medline: 25514302

81. Seto WK, Chan TS, Hwang YY, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. J Clin Oncol 2014;32(33):3736–43. https://doi.org/10.1200/JCO.2014.56.7081. Medline: 25287829

82. Lai KN, Li PK, Lui SF, et al. Membranous nephropathy related to hepatitis B virus in adults. N Engl J Med 1991;324(21):1457–63. https://doi.org/10.1056/NEJM199105233242103. Medline: 2023605

83. Shah AS, Amarapurkar DN. Spectrum of hepatitis B and renal involvement. Liver Int 2018;38(1):23–32. https://doi.org/10.1111/liv.13498. Medline: 28627094

84. Hwang HS, Park CW, Song MJ. Tenofovir-associated Fanconi syndrome and nephrotic syndrome in a patient with chronic hepatitis B monoinfection. Hepatology 2015;62(4):1318–20. https://doi.org/10.1002/hep.27730. Medline: 25645518

85. Hall AM, Hendry BM, Nitsch D, et al. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. Am J Kidney Dis 2011;57(5):773–80. https://doi.org/10.1053/j.ajkd.2011.01.022. Medline: 21435764

86. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology 2009;49(S5):S185–95. https://doi.org/10.1002/hep.22885. Medline: 19399802

87. Custodio JM, Fordyce M, Garner W, et al. Pharmacokinetics and Safety of Tenofovir Alafenamide in HIV-Uninfected Subjects with Severe Renal Impairment. Antimicrob Agents Chemother 2016;60(9):5135–40. https://doi.org/10.1128/AAC.00005-16. Medline: 27216057

88. Post FA, Tebas P, Clarke A, et al. Brief Report: Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Adults With Renal Impairment: 96-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study. J Acquir Immune Defic Syndr 2017;74(2):180–4. https://doi.org/10.1097/QAI.0000000000001186. Medline: 27673443

89. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol 2008;48(2):335–52. https://doi.org/10.1016/j.jhep.2007.11.011. Medline: 18096267

90. Chen YC, Chu CM, Yeh CT, et al. Natural course following the onset of cirrhosis in patients with chronic hepatitis B: a long-term follow-up study. Hepatol Int 2007;1(1):267–73. https://doi.org/10.1007/s12072-007-5001-0. Medline: 19669348

91. Lok AS, McMahon BJ, Brown RS, Jr., et al. Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. Hepatology 2016;63(1):284–306. https://doi.org/10.1002/hep.28280. Medline: 26566246

92. Jang JW, Choi JY, Kim YS, et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. Hepatology 2015;61(6):1809–20. https://doi.org/10.1002/hep.27723. Medline: 25627342

93. Kraut JA, Madias NE. Lactic acidosis. N Engl J Med 2014;371(24):2309–19. https://doi.org/10.1056/NEJMra1309483. Medline: 25494270

94. Idilman R, Akyildiz M, Keskin O, et al. The long-term efficacy of combining nucleos(t)ide analog and low-dose hepatitis B immunoglobulin on post-transplant hepatitis B virus recurrence. Clin Transplant 2016;30(10):1216–21. https://doi.org/10.1111/ctr.12804. Medline: 27409074

95. Cholongitas E, Papatheodoridis GV. High genetic barrier nucleos(t)ide analogue(s) for prophylaxis from hepatitis B virus recurrence after liver transplantation: a systematic review. Am J Transplant 2013;13(2):353–62. https://doi.org/10.1111/j.1600-6143.2012.04315.x. Medline: 23137006

96. Fung J, Wong T, Chok K, et al. Long-term outcomes of entecavir monotherapy for chronic hepatitis B after liver transplantation: Results up to 8 years. Hepatology 2017;66(4):1036–44. https://doi.org/10.1002/hep.29191. Medline: 28370215

97. Klein CG, Cicinnati V, Schmidt H, et al. Compliance and tolerability of subcutaneous hepatitis B immunoglobulin self-administration in liver transplant patients: a prospective, observational, multicenter study. Ann Transplant

2013;18:677–84. https://doi.org/10.12659/AOT.889269. Medline: 24335787

98. Radhakrishnan K, Chi A, Quan DJ, et al. Short Course of Postoperative Hepatitis B Immunoglobulin Plus Antivirals Prevents Reinfection of Liver Transplant Recipients. Transplantation 2017;101(9):2079–82. https://doi.org/10.1097/TP.0000000000001786. Medline: 28880197

99. Bortoluzzi I, Gambato M, Albertoni L, et al. Use of grafts from anti-HBc-positive donors in liver transplantation: a 5-year, single-center experience. Transplant Proc 2013;45(7):2707–10. https://doi.org/10.1016/j.transproceed.2013.07.049. Medline: 24034028

100. Kumar M, Satapathy S, Monga R, et al. A randomized controlled trial of lamivudine to treat acute hepatitis B. Hepatology 2007;45(1):97–101. https://doi.org/10.1002/hep.21486. Medline: 17187417

101. Wiegand J, Wedemeyer H, Franke A, et al. Treatment of severe, nonfulminant acute hepatitis B with lamivudine vs placebo: a prospective randomized double-blinded multicentre trial. J Viral Hepat 2014;21(10):744–50. https://doi.org/10.1111/jvh.12210. Medline: 24329913

102. Singh KP, Crane M, Audsley J, et al. HIV-hepatitis B virus coinfection: epidemiology, pathogenesis, and treatment. AIDS 2017;31(15):2035–52. https://doi.org/10.1097/QAD.0000000000001574. Medline: 28692539

103. Coffin CS, Stock PG, Dove LM, et al. Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV coinfected transplant recipients. Am J Transplant 2010;10(5):1268–75. https://doi.org/10.1111/j.1600-6143.2010.03070.x. Medline: 20346065

104. Konstantinou D, Deutsch M. The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viralinteractions and management. Ann Gastroenterol 2015;28(2):221–8. Medline: 25830779

105. Mucke MM, Backus LI, Mucke VT, et al. Hepatitis B virus reactivation during direct-acting antiviral therapy for hepatitis C: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2018;3(3):172–80. 2018 Jan 19. https://doi.org/10.1016/S2468-1253(18)30002-5.

106. Calvaruso V, Ferraro D, Licata A, et al. HBV reactivation in patients with HCV/HBV cirrhosis on treatment with direct-acting antivirals. J Viral Hepat 2018;25(1):72–9. https://doi.org/10.1111/jvh.12754. Medline: 28703895

107. Lempp FA, Ni Y, Urban S. Hepatitis delta virus: insights into a peculiar pathogen and novel treatment options. Nat Rev Gastroenterol Hepatol 2016;13(10):580–9. https://doi.org/10.1038/nrgastro.2016.126. Medline: 27534692

108. Rizzetto M. The adventure of delta. Liver Int 2016;36 Suppl 1:135–40. https://doi.org/10.1111/liv.13018. Medline: 26725911

109. Noureddin M, Gish R. Hepatitis delta: epidemiology, diagnosis and management 36 years after discovery. Curr Gastroenterol Rep 2014;16(1):365. https://doi.org/10.1007/s11894-013-0365-x. Medline: 24293018

110. Lutterkort GL, Wranke A, Yurdaydin C, et al. Non-invasive fibrosis score for hepatitis delta. Liver Int 2017;37(2):196–204. https://doi.org/10.1111/liv.13205. Medline: 27428078

111. Triantos C, Kalafateli M, Nikolopoulou V, et al. Meta-analysis: antiviral treatment for hepatitis D. Aliment Pharmacol Ther 2012;35(6):663–73. https://doi.org/10.1111/j.1365-2036.2012.04993.x. Medline: 22273482

112. Wedemeyer H, Yurdaydin C, Dalekos GN, et al. Peginterferon plus adefovir versus either drug alone for hepatitis delta. N Engl J Med 2011;364(4):322–31. https://doi.org/10.1056/NEJMoa0912696. Medline: 21268724

113. Heidrich B, Yurdaydin C, Kabacam G, et al. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. Hepatology 2014;60(1):87–97. https://doi.org/10.1002/hep.27102. Medline: 24585488

114. Wranke A, Serrano BC, Heidrich B, et al. Antiviral treatment and liver-related complications in hepatitis delta. Hepatology 2017;65(2):414–25. https://doi.org/10.1002/hep.28876. Medline: 27770553

115. Calle Serrano B, Grosshennig A, Homs M, et al. Development and evaluation of a baseline-event–anticipation score for hepatitis delta. J Viral Hepat 2014;21(11):e154–63. https://doi.org/10.1111/jvh.12251. Medline: 24673975

116. Schwarz KB, Cloonan YK, Ling SC, et al. Children with Chronic Hepatitis B in the United States

and Canada. J Pediatr 2015;167(6):1287–1294 e2. https://doi.org/10.1016/j.jpeds.2015.08.021

117. Marx G, Martin SR, Chicoine JF, et al. Long-term follow-up of chronic hepatitis B virus infection in children of different ethnic origins. J Infect Dis 2002;186(3):295–301. https://doi.org/10.1086/341508. Medline: 12134225

118. Wu JF, Tsai WY, Hsu HY, et al. Effect of puberty onset on spontaneous hepatitis B virus e antigen seroconversion in men. Gastroenterology 2010;138(3):942–8 e1. https://doi.org/10.1053/j.gastro.2009.11.051. Medline: 19962986.

119. Yang HI, Hung HL, Lee MH, et al. Incidence and determinants of spontaneous seroclearance of hepatitis B e antigen and DNA in patients with chronic hepatitis B. Clin Gastroenterol Hepatol 2012;10(5):527–34 e1–2. Medline: 22178461.

120. Chiu YC, Liao SF, Wu JF, et al. Factors affecting the natural decay of hepatitis B surface antigen in children with chronic hepatitis B virus infection during long-term follow-up. J Pediatr 2014;165(4):767–72 e1. https://doi.org/10.1016/j.jpeds.2014.06.059. Medline: 25112693.

121. Xue MM, Glenn JS, Leung DH. Hepatitis D in Children. J Pediatr Gastroenterol Nutr 2015;61(3):271–81. https://doi.org/10.1097/MPG.0000000000000859. Medline: 25988557

122. Bortolotti F, Guido M, Bartolacci S, et al. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. Hepatology 2006;43(3):556–62. https://doi.org/10.1002/hep.21077. Medline: 16496323

123. McMahon BJ, Holck P, Bulkow L, et al. Serologic and clinical outcomes of 1536 Alaska Natives chronically infected with hepatitis B virus. Ann Intern Med 2001;135(9):759–68. https://doi.org/10.7326/0003-4819-135-9-200111060-00006. Medline: 11694101

124. 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(3):805–10. https://doi.org/10.1016/0016-5085(90)90972-4.

125. Evans AA, Fine M, London WT. Spontaneous seroconversion in hepatitis B e antigen-positive chronic hepatitis B: implications for interferon therapy. J Infect Dis 1997;176(4):845–50. https://doi.org/10.1086/516538. Medline: 9333140

126. Bertoletti A, Kennedy PT. The immune tolerant phase of chronic HBV infection: new perspectives on an old concept. Cell Mol Immunol 2015;12(3):258–63. https://doi.org/10.1038/cmi.2014.79. Medline: 25176526

127. Jonas MM, Chang MH, Sokal E, et al. Randomized, controlled trial of entecavir versus placebo in children with hepatitis B envelope antigen-positive chronic hepatitis B. Hepatology 2016;63(2):377–87. https://doi.org/10.1002/hep.28015. Medline: 26223345

128. 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(6):2018–26. https://doi.org/10.1002/hep.25818. Medline: 22544804