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Chronic hepatitis B in British Columbia

Chronic hepatitis B, a complex viral infection, requires longitudinal follow-up, management, and often clinical judgment on a case-to-case basis because a patient's test results may not fit perfectly within any particular phase of infection.

ABSTRACT: Chronic hepatitis B is caused by the hepatitis B virus, a member of the Hepadnaviridae family. It is a common infection with a worldwide prevalence of more than 250 million people. In Canada and British Columbia, it disproportionately affects immigrant groups from endemic countries, Indigenous populations, and people who inject drugs. Pregnant women in BC are universally screened for hepatitis B virus, and if positive, measures are taken to reduce vertical transmission to the neonate. Canada has a universal vaccination program for hepatitis B virus, and BC currently provides routine immunizations to neonates at 2, 4, and 6 months. The current focus for treatment of chronic hepatitis B is to prevent progression of liver inflammation and fibrosis and to prevent hepatocellular carcinoma. There currently are no treatment options that result in the complete cure of chronic hepatitis B.

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Chronic hepatitis B is caused by a small DNA virus called hepatitis B virus (HBV), a prototype member of the Hepadnaviridae family and the *Orthohepadnavirus* genus that infects mammals.[1] Chronic hepatitis B has a worldwide prevalence of more than 250 million people.[2] Areas with high endemicity include Asia, Africa, and parts of South America. In Canada, up to 480 000 people may be infected.[3,4] The population groups with the highest infection rates include immigrants from endemic countries, Indigenous people, and people who inject drugs.[4] In BC, local epidemiology is driven primarily by a large immigrant population from endemic countries in Asia.[3] In many endemic countries, routine screening and prophylaxis of infants at birth may not have been widely available. These individuals often become chronically infected during the perinatal period or in early childhood, as transmission during the neonatal period or at a young age leads to the highest rates of chronic infection.[5,6] Other modalities of HBV transmission include percutaneous, sexual, or close person-to-person contact through open cuts or sores. Infectious bodily fluids with the highest concentrations of HBV are blood, followed by semen and vaginal fluids; much lower concentrations are found in saliva secretions, and transmission is not attributable to sharing utensils.[7] In BC, most chronic hepatitis B cases are among East and South Asian individuals who have very low levels of illicit drug or alcohol use, major mental illness, or co-infection with HIV or hepatitis C.[8] In contrast, acute hepatitis B diagnoses in BC are more often associated with individuals who have a high level of substance use and co-infection with HIV or hepatitis C, and with predominantly young Caucasian males.[8]

Within Asian immigrant populations in BC, knowledge of chronic hepatitis B infection, especially in relation to routes of transmission, was found to be limited.[9] A more recent study of a mix of Asian communities in BC, including Chinese, Korean, Filipino, South Asian, and Southeast Asian ethnic groups, showed that hepatitis B awareness was lowest in the South Asian communities.[10] This is a concern because HBV is the most common cause of hepatocellular carcinoma in Asian North Americans.[11]

Testing for hepatitis B

The Canadian Association for the Study of the Liver guidelines recommend that those who are in high-risk groups be screened for HBV.[12] They include immigrants from intermediate- to high-risk countries and infants whose parents are from endemic countries and are not vaccinated **[Table 1]**. It is also recommended that at-risk individuals who have not received routine HBV vaccination be vaccinated if they screen negative for HBV.[12] The BC Centre for Disease Control *Communicable Disease Control Manual* lists groups that are recommended to receive free hepatitis B vaccination.[13] A study conducted in BC from 2006 to 2009 showed that only 71% of the study group's 759 adult immigrants, whose additional language was English, had undergone HBV testing, 8% had received vaccination without testing, and 21%

TABLE 1. At-risk groups for whom routine screening for hepatitis B virus (HBV) is recommended.

- People who were born or have resided in regions where HBV is more common (Asia, Australasia, Eastern Europe, South America, Africa, Middle East).
- Household contacts with HBV carriers.
- Sexual contacts with HBV carriers, persons with multiple sexual partners.
- People who inject illicit drugs or use them intranasally (past or present).
- People who are incarcerated.
- Patients with renal failure who require dialysis.
- Patients with signs of liver disease (i.e., abnormal liver enzyme test) or other infections (i.e., hepatitis C, HIV).
- Pregnant women.
- Patients requiring immunomodulation therapy or those who will develop immunosuppression.

Adapted from "Management of hepatitis B virus infection: 2018 guidelines from the Canadian Association for the Study of Liver Disease and Association of Medical Microbiology and Infectious Disease Canada."[12]

had neither undergone testing nor received vaccination.[14] The authors suggested that better identification and management of chronic hepatitis B carriers was needed to improve strategies for reducing HBV transmission to others.[9,14] In BC, it is recommended that all pregnant women receive prenatal screening for HBV with hepatitis B surface antigen (HBsAg) during every pregnancy.[12,13] It is estimated that 95% to 99% of all pregnant women are routinely screened, and that 0.7% to 1.2% screen positive for HBsAg.[13]

Clinical presentation of chronic hepatitis B

The likelihood of developing chronic hepatitis B after an exposure to HBV is highly dependent on the patient's age. Patients who acquired HBV via vertical transmission in infancy have more than a 90% risk of developing chronic infection, but this risk decreases to less than 5% in patients who are exposed to HBV as an adult. In the latter scenario, over 95% of those infected will transition to resolved infection state (HBsAg loss).[12] Acute hepatitis B is usually a subclinical or self-limited illness, but in less than 1% cases, it can result in severe hepatitis and fulminant liver failure.[12]

Chronic hepatitis B is defined as having a positive HBsAg for 6 months or longer.[15] Most patients with chronic hepatitis B are asymptomatic until the liver disease becomes advanced and there is evidence of cirrhosis, or if there are extrahepatic manifestations. Some patients may also report nonspecific symptoms such as fatigue. Physical examination is often normal, but physicians should pay special attention to assessing for stigmata of chronic liver disease.

TABLE 2. Clinical phases in chronic hepatitis B, corresponding lab work, and serological and diagnostic tests.

Clinical phase	HBeAg*–positive chronic infection	HBeAg–positive chronic hepatitis	HBeAg–negative chronic infection	HBeAg–negative chronic hepatitis	HBsAg* negative
Synonymous terminology	• Immune tolerant	• Immune active	• Low replicative chronic HBV • Inactive carrier		• Resolved hepatitis B infection • Occult hepatitis B • Functional cure
• **HBsAg***	+	+	+	+	–
• **HBeAg***	+	+	–	–	–
• **Anti-HBc***	+	+	+	+	+
• **Anti-HBe***	–	–	+	+	+
• **Anti-HBs***	–	–	–	–	+/–
Alanine aminotransferase (ALT)	Normal	Elevated or fluctuating	Normal	Elevated or fluctuating	Normal
HBV DNA (IU/mL)	$> 10^7$	10^4–10^7	Often < 2000	10^3–10^7	Undetectable
FibroScan	Normal	Abnormal	Usually normal	Abnormal	Normal
Monitoring lab work[†‡]	ALT and HBV DNA every 3–6 months HBeAg every 6–12 months	ALT and HBV DNA at 3 and 6 months, then every 3–6 months[§] HBeAg every 3–6 months	ALT and HBV DNA every 6–12 months HBsAg every 12 months	ALT and HBV DNA at 3 and 6 months, then every 3–6 months[§] HBsAg every 12 months	No routine lab work
Treatment recommended	No[‖¶]	Yes	No[‖]	Yes	No[‖]
Referral to specialist	Optional	Recommended	Optional	Recommended	No[#]

Note: Above parameters presume no other coexisting liver comorbidities.

* HBeAg: hepatitis B e-antigen; HBsAg: hepatitis B surface antigen; anti-HBc: hepatitis B core antibody; anti-HBe: hepatitis B e-antibody; anti-HBs: hepatitis B surface antibody

† Recommendations for lab work are variable and ultimately depend on specific patient characteristics, results and stability of previous tests, other liver comorbidities, etc.

‡ Renal function lab work monitoring is recommended if using tenofovir disoproxil fumarate or adefovir

§ Monitoring lab work can be done every 6 months if using more potent antivirals (i.e., tenofovir disoproxil fumarate or entecavir), or every 3 months if using less potent agents (i.e., lamivudine)

‖ No treatment would generally be recommended unless there was immunosuppression. Degree of immunosuppression and current phase of infection help determine whether prophylactic treatment is warranted

¶ Prophylactic treatment in pregnancy would be considered

Referral may be indicated if patient to undergo immunosuppressive treatment

Extrahepatic manifestations are thought to be due to circulating immune complexes, and the most common attributable to chronic hepatitis B are polyarteritis nodosa and membranous nephropathy.[16] Polyarteritis nodosa is a systemic necrotizing vasculitis that usually affects medium-sized arteries but sometimes can also affect small arteries. Most cases of polyarteritis nodosa are idiopathic, but traditionally, up to approximately 35% of total cases were thought to be associated with HBV.[17] However, with the introduction of the HBV vaccine and antiviral agents, HBV is now thought to be responsible for a much lower proportion of total cases. The classical presentation of membranous nephropathy is nephrotic range proteinuria. In children, papular acrodermatitis can occur, which causes maculopapular, erythematous, and nonpruritic lesions involving the face and extremities.[16,18] Only a small number of patients may recall a preceding history of acute hepatitis prior to being diagnosed with chronic hepatitis B. A serum sickness-like syndrome with fever, rash, and polyarteritis can occur during this phase of illness and usually precedes the onset of jaundice.[16,19]

Treatment and prevention of chronic hepatitis B

Treatment goals of chronic hepatitis B have traditionally been to prevent progression of chronic inflammation to higher levels of fibrosis, and to prevent cirrhosis and hepatocellular carcinoma. The American Association for the Study of Liver Diseases, the Asian Pacific Association for the Study of the Liver, the Canadian Association for the Study of the Liver, and the European Association for the Study of the Liver all publish detailed guidelines on the treatment and management of hepatitis B.[12,15,20,21] **Table 2** summarizes the various phases of chronic hepatitis B and situations where antiviral treatment is generally recommended. An assessment of fibrosis that is performed noninvasively is generally recommended for all patients and can be done various ways, including by FibroScan or aspartate aminotransferase to platelet ratio index score.

Within Canada, reimbursement criteria and access to antiviral agents for the treatment of hepatitis B are quite variable among jurisdictions.[3] In BC, reimbursable prescription drug coverage through application for special authority request previously covered only lamivudine as a first-line option and pegylated interferon alpha in a few selected scenarios. In November 2018, BC PharmaCare added tenofovir disoproxil fumarate and entecavir as first-line options along with lamivudine. In BC, tenofovir alafenamide is not currently a covered benefit drug for the treatment of HBV, although that may change in the future. Tenofovir alafenamide is a prodrug, and has an improved side effect profile in terms of renal function and bone turnover when compared with tenofovir disoproxil fumarate.[21] Usual dosage information, potential side effects, and recommended monitoring of these HBV antiviral medications are listed in **Table 3**. In BC, application for special authority coverage for chronic hepatitis B medications is open to all medical practitioners and is not restricted to specific specialists. Clinical criteria that need to be met include an alanine aminotransferase greater than the upper limit of normal and HBV DNA greater than 2000 IU/mL. Alternatively, medication coverage is also available if there is evidence of fibrosis with stage equal to or greater than F2, which can be deduced through FibroScan, aspartate aminotransferase to platelet ratio index, or liver biopsy. If there are circumstances in which a provider wants to prescribe antivirals for hepatitis B that are not covered by the listed indications, such as for prophylaxis in the setting of immunosuppression, additional information can be submitted along with the special authority application for consideration by the BC Hepatitis Drug Benefit Adjudication Advisory Committee.

Oral medications for chronic hepatitis B are usually well tolerated, although they often need to be taken for prolonged periods and sometimes indefinitely to prevent viral reactivation. Stopping treatment is possible for those who have hepatitis B e-antigen (HBeAg)-positive chronic hepatitis if they subsequently convert to anti-HBe positive, which suggests transition to HBeAg-negative chronic infection (also known as low replicative chronic HBV infection or inactive carrier), as long as there is close monitoring for relapse thereafter. For patients with HBeAg-negative chronic hepatitis, treatment is often indefinite. There are indicators for when antiviral medications can potentially be stopped based on close observation, such as if there is persistent loss of HBsAg; however, generally, these are the

TABLE 3. Dosing of common hepatitis B virus antiviral therapies.

	Dose in adults*	Potential side effects	Monitoring on treatment
Lamivudine	100 mg daily	Pancreatitis Lactic acidosis	• Amylase or lactic acid level if clinical concern
Entecavir	0.5 mg daily (1 mg daily)†	Lactic acidosis (decompensated cirrhosis only)	• Lactic acid level if clinical concern
Tenofovir disoproxil fumarate	300 mg daily	Nephropathy Fanconi syndrome Osteomalacia Lactic acidosis	• Baseline serum creatinine and phosphate, urine glucose and protein at baseline and then at least annually • Consider bone density study at baseline and during treatment in those with fractures or risk factors for osteopenia • Lactic acid if clinical concern
Tenofovir alafenamide‡	25 mg daily	Lactic acidosis	• Baseline serum creatinine and phosphate, urine glucose and protein at baseline and then as needed • Lactic acid if clinical concern

* Dosing adjustments needed in renal dysfunction

† If lamivudine experienced or have decompensated cirrhosis

‡ Not currently a covered benefit drug for HBV treatment in BC, Canada

Adapted from "Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance"[21]

exception rather than the rule. Newer medications such as tenofovir disoproxil fumarate, tenofovir alafenamide, and entecavir have low rates of resistance, even with prolonged use. For patients who have developed resistance to other medications, tenofovir disoproxil fumarate or tenofovir alafenamide is typically the drug of choice. Long-term use of tenofovir disoproxil fumarate is generally not recommended for patients with chronic kidney disease or osteoporosis because it can worsen renal function and reduce bone mineral density. According to the 2017 European Association for the Study of the Liver guidelines, tenofovir alafenamide is recommended over tenofovir disoproxil fumarate in patients older than 60 years, those with bone disease (chronic steroid use or medications that worsen bone density, history of fragility fracture, osteoporosis), and those with renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 m^2, albuminuria > 30 mg/24 h, moderate dipstick proteinuria, low phosphate < 2.5 mg/dl, or dialysis patients).[20] Pegylated interferon alfa has sometimes been used because it has a finite duration of treatment, although sustained response rates occur only in a minority of patients, and the medication is associated with significant side effects and is contraindicated in patients with cirrhosis.

For pregnant patients who screen positive for HBsAg, ordering HBV DNA viral load is recommended to determine if further antiviral prophylaxis is required during pregnancy to reduce perinatal HBV transmission **[Figure]**.[12] The 2017 Society of Obstetricians and Gynaecologists of Canada guidelines provide a level II-B recommendation for starting antiviral treatment in pregnant patients with HBV DNA viral load greater than 200 000 IU/mL starting in the third trimester (around 28 to 32 weeks) until delivery.[22] Typically, tenofovir disoproxil fumarate is chosen because of its safety in pregnancy and high barrier to developing resistance. In addition, to reduce the risk of HBV transmission from HBsAg-positive parents to infants, hepatitis B immune globulin (HBIg) 0.5 mL intramuscular injection along with HBV vaccine 0.5 mL intramuscular injection is recommended as prophylaxis for the infant after birth.[13] If the mother is not HBsAg positive but the father or another household contact has chronic hepatitis B, then HBV vaccine 0.5 mL intramuscular injection is recommended for the infant after birth, but not HBIg.[13] Of note, all infants in BC are vaccinated for HBV as part of the diphtheria, tetanus, pertussis, hepatitis B, polio, and *Haemophilus influenzae* type B (DTaP-HB-IPV-Hib) vaccine series given at ages 2, 4, and 6 months. The prophylaxis given at birth to high-risk infants is in addition to the routine immunizations given; thus, these infants receive four doses of hepatitis B vaccination in total.

In Canada, BC was the first province to adopt a routine school-based program for HBV vaccination, which started in 1992.

Screening for hepatocellular carcinoma is an important aspect of management. The Canadian Association for the Study of the Liver guidelines recommend surveillance ultrasound screening every 6 months for those who are at high risk. High-risk groups include Asian men aged 40 years or older, Asian women 50 years or older, African people aged 20 years or older, cirrhotic patients, those with a family history of hepatocellular carcinoma (starting at age 40 years), and all HIV-co-infected patients (starting at age 40 years).[12] If ultrasound is not available, then alpha-fetoprotein can be used, but it has comparably lower sensitivity and specificity.[21]

Goals and future targets for chronic hepatitis B

The United Nations' goal for HBV is to reduce new cases of HBV by 90% by 2030 (equivalent to 0.1% prevalence HBsAg in children).[23,24] As of 2015, the World Health Organization reported that 185 (95% of all) countries have incorporated HBV vaccination into their national infant immunization schedule.[23,24] In Canada, BC was the first province to adopt a routine school-based program for HBV vaccination, which started in 1992; all other provinces did so in 1998. Several provinces have now moved to a routine infant or birth HBV vaccination program; BC made this switch in 2001.

Future targets for HBV treatment will include a functional cure and, subsequently, a

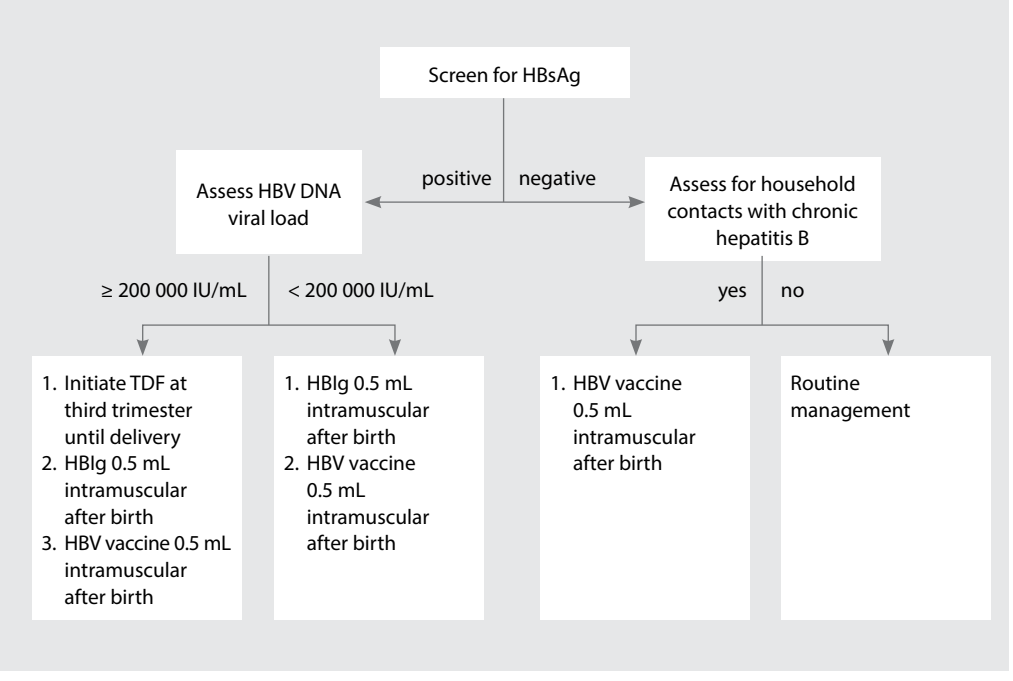

FIGURE. Screening and management of pregnant hepatitis B-positive patients (HBsAg: hepatitis B surface antigen; HBIg: hepatitis B immune globulin; TDF: tenofovir disoproxil fumarate).

complete cure. A functional cure will allow suppression of HBV DNA and normalization of alanine aminotransferase at the end of treatment, with a loss of HBsAg. However, covalently closed circular DNA would not be eliminated in this situation; thus, there is the ongoing risk of HBV reactivation with immunosuppression. A complete cure will result in permanent HBV DNA suppression and normalization of alanine aminotransferase with the elimination of covalently closed circular DNA. Of note, neither strategy targets HBV DNA integration, and thus does not necessarily prevent hepatocellular carcinoma unless HBV treatment is initiated early before integration has occurred.[25] Several direct-acting drugs that target different aspects of the HBV life cycle are currently in development, although most are in preclinical phases or early phase clinical trials. These include molecules targeting viral entry, covalently closed circular DNA, capsid inhibitors, and HBsAg release inhibitors.[26,27]

Summary

Chronic hepatitis B is a complex viral infection that requires longitudinal follow-up and management. Important clinical phases and recommended investigations for chronic hepatitis B are summarized in **Table 2**. Detailed management algorithms are outside the scope of this review but are well summarized in various international guidelines.[12,15,20,21] Not uncommonly, a patient's test results may not fit perfectly within any particular phase, and clinical judgment on a case-to-case basis is often required. Referral to an infectious diseases or hepatology specialist is reasonable, especially in situations where consideration of antiviral treatments may be warranted. ■

Competing interests

None declared.

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