Pharmacy FAQ

Hepatitis B reactivation and screening

1. What is Hepatitis B and Hepatitis B reactivation?[1,2]

Hepatitis B is the liver infection caused by Hepatitis B Virus (HBV), a DNA virus that can result in chronic liver disease. It is transmitted mainly by infected blood or body fluids primarily through perinatal, percutaneous or sexual exposure. Household contacts are considered at increased risk, as well as individuals born in intermediate/high HBV endemic regions. Chronic HBV infection is the leading cause of liver cancer and liver transplantation in Canada.

The clinical presentation of HBV can vary from asymptomatic hepatitis to potentially fatal fulminant hepatic failure. Less than 10% of children and approximately 30-50% of adults with acute infection experience symptoms. Elevated liver chemistry and presence of serologic HBV markers are still detected in asymptomatic individuals. These markers include HBV antigens, antibodies to the antigens and HBV DNA.

About 95% of infected immune competent adults clear the virus within 6 months, become Hepatitis B surface antigen (HBsAg) negative and develop antibodies to the surface antigen (HBsAb positive). Adults who cannot clear the virus, will remain HBsAg positive and will be a chronic carrier. These adults are typically immunocompromised and/or have other viral co-infections such as HIV, Hepatitis C or Hepatitis D. All individuals who have had or are carrying HBV, test positive for Hepatitis B core antibodies (HBcoreAb). Of note, latent HBV remains in the liver, even after cleared infection, placing anyone with a history of HBV infection at risk of HBV “reactivation”.

Hepatitis B reactivation is the increase in HBV replication in individuals with a chronic or resolved HBV infection. Risk factors include certain host factors (male, advanced age, cirrhosis and type of cancer), degree and type of immunosuppressive therapy, and status of the hepatitis B infection or co-infection. HBV replication is sometimes described as a two-phase process:

1) If the immune system is suppressed (e.g., initiation of immunosuppressive therapy):
   - host immunity against HBV is decreased
   - HBV replication and hepatocyte HBV-antigen expression are increased
2) When the immune system recovers (e.g., withdrawal of immunosuppressive therapy):
   - host immunity against HBV is increased
   - immunocompetent cells attack the hepatocytes that had become HBV antigen-laden, resulting in elevation of ALT (ALT "flare") and liver injury

Hepatitis B reactivation may occur spontaneously or whenever an individual with past or chronic HBV infection becomes immunosuppressed, receives treatment with or completes immunosuppressive therapy, recovers from immunosuppression, or completes antiviral therapy. It is usually associated with increasing or fluctuating ALT and HBV DNA levels.

2. Why are cancer patients screened for Hepatitis B Virus (HBV)?[1,3,4]

Cancer patients may be unaware of past asymptomatic HBV infection and are at increased risk of HBV reactivation depending on their type of cancer, choice of anticancer therapy (including radiation therapy and transarterial chemoembolization) and extent of immunosuppression. HBV reactivation can be prevented by screening and appropriate antiviral prophylaxis or monitoring.

HBV reactivation has been well documented in HBV patients with hematologic malignancy. The risk of reactivation for these patients is about 48% with chronic HBV and about 18% with past HBV. The HBV reactivation risk is less for HBV patients with solid tumours and has been less studied.

The risk of HBV reactivation with cancer medication is usually classified as low (< 1%), moderate (1-10%), and high (> 10%), although there are a group of these patients that are in a very high risk group.

Patients receiving **B-cell depleting therapy** are at **very high risk** for HBV reactivation of their chronic HBV or past HBV. The BC Cancer Protocol Summary for Hepatitis B Virus Reactivation Prophylaxis (SCHBV) activated Sep 1 2023, lists examples of B-Cell depleting cancer therapies. These therapies include various anti-B-cell or plasma cell monoclonal antibodies (e.g., daratumumab, rituximab), bi-specific antibodies (e.g., blinatumomab), bruton's tyrosine kinase (BTK) inhibitors (e.g., ibrutinib, acalabrutinib) and chimeric antigen receptor T-cell (CAR T-cell) therapy.

All patients receiving **autologous or allogeneic hematopoietic stem cell transplant** are considered at **high risk** for HBV reactivation of their chronic HBV or past HBV.

Patients receiving **anthracyclines** or **high-dose corticosteroids** (prednisone equivalent ≥ 20 mg/day for ≥ 4 weeks) who have chronic HBV (HBsAg positive) are considered at **high risk** for HBV reactivation**,** while patients receiving these therapies who had past HBV (HBsAg negative, HBcoreAb positive) are considered at **moderate risk.**

3. Who should be screened?[3,4]

HBV screening is recommended for any cancer patient at increased risk of HBV reactivation prior to receiving immunosuppressive therapy.

BC Cancer has incorporated routine HBV screening in the relevant hematologic protocols found in the Lymphoma, Myeloma and Leukemia protocol summaries. Some patients with hematologic malignancies are at a particularly high risk for reactivation due to their exposure to the immunosuppressive effects of both cancer treatment and their disease. As described above, assessment of HBV reactivation risk in individuals with chronic or previous HBV infection is based on treatment regimen risk. Hormonal therapy is unlikely to increase the risk of HBV reactivation risk. HBV serology testing is used to identify patients at risk for reactivation.

4. How do you interpret the results of the Hepatitis B screening tests?[2,4,5,6,7]

Hepatitis B serology testing can be used to identify patients at risk for HBV reactivation by measuring serum concentrations of HBV-specific antigens and antibodies (see Table 1). Different combinations of serology markers are used to determine the clinical status of the hepatitis B infection (see Table 2).

HBsAg, HBcoreAb (Anti-HBc) and HBsAb (Anti-HBs) are hepatitis B screening tests required at baseline for select Lymphoma, Myeloma and Leukemia protocols. Patients that test positive for HBsAg and/or HBcoreAb will also require a baseline HBV DNA test.

Hepatitis B Screening

Table 1. Common Hepatitis B Serology Markers

Marker	Definition	Note
HBsAg	Hepatitis B surface antigen	▪ **General marker of Hepatitis B infection** ▪ Usually disappears in 4 to 6 months after acute infection ▪ Persistence for > 6 months suggests chronic infection
HBcoreAb or Anti-HBc ▪ IgM anti-HBc ▪ IgG anti-HBc	Hepatitis B core antibody	▪ **Confirmed prior exposure to HBV** (resolved, acute or chronic infection) ▪ IgM anti-HBc: Acute Hepatitis B infection (usually disappears within 6 months)* ▪ IgG anti-HBc: Resolved or chronic Hepatitis B infection
HBsAb or Anti-HBs	Hepatitis B surface antibody	▪ Immunity to Hepatitis B from resolved infection or from vaccination
HBV DNA	Hepatitis B DNA Viral load	▪ Therapeutic monitoring of chronic HBV infection ▪ Magnitude of HBV replication and risk of disease progression ▪ Predictor of cirrhosis and hepatocellular carcinoma

* IgM anti-HBc can remain positive for many years in some chronically infected patients or in chronically infected patients during HBV reactivation

Table 2. Interpretation of Hepatitis B Serology Test Results

Tests	Results	Interpretation	At Risk For Reactivation
HBsAg	–	Susceptible to future hepatitis infection	No
Anti-HBc	–		
Anti-HBs	–		
HBsAg	–	Immune due to natural infection	**Yes**
Anti-HBc	**+**		
Anti-HBs	+		
HBsAg	–	Immune due to hepatitis B vaccination	No
Anti-HBc	–		
Anti-HBs	+		
HBsAg	**+**	Acutely infected	**Yes**
Anti-HBc	**+**		
IgM anti-HBc	+		
Anti-HBs	–		
HBsAg	**+**	Chronically infected	**Yes**
Anti-HBc	**+**		
IgM anti-HBc	–		
Anti-HBs	–		
HBsAg	–	Four Possible Interpretations: 1. Resolved infection [a] (most common) 2. False positive anti-HBc, thus susceptible 3. 'Low level' chronic infection [b] 4. Resolving acute infection [c]	**Yes**
Anti-HBc	**+**		
Anti-HBs	–		

a After many years of acute hepatitis B recovery, anti HBs may fall to undetectable levels
b After many years of chronic hepatitis B infection, HBsAg may fall to undetectable levels
c May occur in patients with fulminant hepatitis B where virus clearance tends to be more rapid. During this window, HBsAg may disappear while anti-HBs is still not detected. The sole marker that indicates acute hepatitis B infection is the presence of IgM anti-HBc.

5. How do you minimize the risk for Hepatitis B reactivation?[2,4,7,8,9]

The SCHBV protocol outlines the current baseline tests, reactivation risk assessment, antiviral prophylaxis and monitoring for patients undergoing systemic therapy for lymphoid, plasma cell and myeloid malignancies. The BC Cancer Lymphoma, Myeloma and Leukemia protocols are in the process of being updated with reference to this protocol.

See the ***Appendix: Risk of hepatitis B reactivation with immunosuppressive therapy*** in the SCHBV protocol. The prescribed cancer treatment regimen is used to determine reactivation risk and whether monitoring alone or added antiviral prophylaxis is recommended. Level of risk also determines how long the prophylactic antiviral and/or monitoring will continue after cancer therapy has been completed.

Monitoring

The **Tests** section of the SCHBV protocol outlines the hepatitis B screening tests recommended at baseline for select protocols: HBsAg, HBcoreAb (Anti-HBc) and HBsAb (Anti-HBs). Patients who test positive for either HBsAg or HBcoreAb during baseline testing, also require a baseline HBV DNA test.

A positive HBsAg result (**HBsAg reactive**) usually indicates active HBV infection, and ongoing monitoring of HBV DNA and ALT every 3 months and for at least 12 months after stopping antivirals is recommended. HBV DNA reflects viral load and ALT is a liver enzyme that can indicate liver inflammation although it does not always correlate with disease severity.

Individuals with past HBV that has resolved may test negative for HBsAg but positive for HBcoreAb (**HBsAg nonreactive, HBcoreAb reactive**). They will require monitoring of HBsAg, along with HBV DNA and ALT as above, for possibility of change to HBsAg positive status.

A hepatology specialist should be consulted for co-managing patients with liver fibrosis or cirrhosis, when monitoring is challenging, if HBV DNA level rises or if a HBsAg negative patient becomes positive.

Antiviral prophylaxis

The antivirals recommended for HBV prophylaxis are entecavir and tenofovir. Entecavir 0.5 mg PO daily is preferred; it requires dose modifications for altered kidney function. An alternative to entecavir is tenofovir disoproxil fumarate (Viread®-type) 300 mg PO daily, which can cause renal toxicity and also requires dose modifications for altered kidney function. Antiviral prophylaxis will continue during and from 6 to 18 months after completion of cancer treatment, depending on cancer treatment regimen.

Entecavir and tenofovir are PharmaCare benefits requiring exceptional Special Authority approval when antiviral prophylaxis is recommended. The new BC Cancer guidelines in the SCHBV protocol have been developed after discussion with PharmaCare. PharmaCare will no longer be approving Special Authority requests for lamivudine for

antiviral prophylaxis or any antiviral prophylaxis for patients with lower risk of HBV reactivation. Switching from lamivudine to another antiviral can occur at next Special Authority renewal.

References:

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