HEPATITIS B MANAGEMENT

Background
Chronic Hepatitis B Virus (HBV) infection had an estimated prevalence in Australia of 0.7-0.8% in 2002 (1). Prevalence is highest in people born in much of Asia and Africa (above 8%), and amongst Indigenous Australians. Migrants and Indigenous people account for the majority of chronic HBV infections in Australia. (2)

Most people with HBV infection are asymptomatic and it is estimated that 60,000 of the estimated 160,000 Australians chronically infected have not been diagnosed (1, 3). All patients with chronic HBV infection are at risk of reactivation hepatitis B disease during immunosuppression with chemotherapy, which is associated with significant morbidity and mortality(4, 5).

Reactivation hepatitis B disease is a spectrum of illness ranging from asymptomatic increase in viral replication through acute fulminant hepatitis requiring transplantation or causing death.

The risk of reactivation varies with the intensity of the chemotherapy. Treatment of haematological malignancy (and stem cell transplantation) involves a higher risk (38-48%) than treatment of solid tumours (approximately 15%, although risk in breast cancer treatment may be higher)(6). Higher risk has also been reported in patients receiving glucocorticoids as these agents act directly on the virus to enhance replication (7).

Prophylactic treatment with antiviral medication during and after chemotherapy greatly reduces the risk of viral reactivation and subsequent hepatitis and is associated with a reduction in mortality (4, 8, 9). Antivirals with a high barrier to resistance, such as entecavir or tenofovir, have recently been shown to be more effective than drugs with a lower barrier to resistance such as lamivudine even when used in patients with low HBV viral loads and as such should be preferred. If patients are HBeAg positive or have detectable HBV DNA at baseline, they will require long-term therapy (lamivudine is not appropriate in this setting due to the high risk of development of resistance).

The highest risk of severe illness is in patients who are; young, male, HBeAg(+), have high HBV DNA load (>10^4 copies/ml), more severe immune suppression or pre-existing cirrhotic liver disease. It is important to recognize fatal flares in HBV have been reported in patients with none of these risk factors (6).

Screening:
1. All haematology patients attending the Victorian Comprehensive Cancer Centre for systemic cancer chemotherapy or any other immunosuppressive therapy should be screened for HBV infection, regardless of their apparent risk factors. The following tests should be requested.
   a. Serum Hepatitis B Surface Antigen (HBsAg)
   b. Serum Hepatitis B Core Antibody (anti-HBcAb)
   c. Serum Hepatitis B surface antibody (antiHBsAb)

2. Oncology patients who are undergoing chemotherapy with curative intent, chemotherapy containing anthracyclines or prednisolone equivalents of >20 mg/day for > 1month or where the treating physician is concerned about hepatitis B risk. The following test should be requested
   a. Serum Hepatitis B Surface Antigen (HBsAg)
Management:

Patients with a positive antiHBcAb or HBsAg should be referred for infectious diseases advice (either as inpatients or outpatients) **prior to commencing chemotherapy**.

**All patients with a positive HBsAg** should have:

- Full hepatitis serology performed (anti-HBcAb, anti-HBsAb, HBeAg, anti-HBeAb, HBeAg and screening for HAV, HCV, HDV and HIV)
- Quantitative HBV DNA should be tested if HBsAg or anti-HBc are positive regardless of antiHBs level.
- A Fibroscan pre chemotherapy should be performed (if possible) to assess for the presence and degree of liver damage. [Booking form for RMH](#)
- Pre-existing compensated cirrhosis is a relative contraindication to myeloablative therapy and needs to be considered on a case by case basis.
- HBsAg(+) without advanced liver fibrosis is not a contraindication to transplant but requires specific management to prevent reactivation of HBV.
- Consider conditioning regimens with less hepatotoxicity if LFTs are abnormal but not at risk of impairing treatment outcome
- Prophylaxis/Treatment for chronic HBV should be commenced at least 1 week prior to commencement of chemotherapy (see algorithm below).

Further assessment regarding the stage of hepatitis B disease (liver workup) should include:

1. Liver imaging (if not already performed)
2. Alpha fetoprotein
3. Consideration of possible need for liver biopsy
4. Check immunity (Hepatitis A, Hepatitis D) and vaccinate for Hepatitis A virus (if not immune)

**Patients with markers of prior HBV infection (HBsAg-, anti HBcAb+):**

- Patients who have markers of prior Hepatitis B never completely clear virus, even if they are anti-HBs positive. This represents a very low replicative state controlled by the host immune system which doesn’t normally cause disease, but can reactivate if the patient is immunosuppressed.
- All patients who are anti-HBcAb positive should have HBV DNA performed to determine if they have occult HBV and patients with detectable HBV DNA should receive antiviral prophylaxis as for HBsAg positive patients
- The reactivation rate in these patients is much lower than HBsAg positive patients and risk is dependent of type of immunosuppressive therapy and HBsAb levels (see algorithm below).
Screen patients for HBV:
Haematology: HBsAg, HBCAb, HBsAb
Oncology: HBsAg

HBsAg positive

Chronic HBV
Referral to Infectious Diseases Unit required
Measure HBV viral load, complete workup*

If HBV viral load ≥ 2000 IU/ml
Commence HBV treatment
Entecavir > 1 week prior to chemotherapy

Continue HBV treatment post completion of immuno-suppressive therapy
Likely lifelong
Aim:
Undetectable HBV VL
HBeAg seroconversion
Normalisation of ALT

Monitor patients with LFTs, HBV viral load 3 monthly whilst on treatment/prophylaxis and for 12 months post cessation of prophylaxis

If HBV viral load < 2000 IU/ml
Commence HBV prophylaxis
Entecavir > 1 week prior to chemotherapy

Continue HBV prophylaxis for 6 to 12 months post completion of immuno-suppressive therapy
HBV prophylaxis should continue if there is ongoing immuno-suppression

Resolved HBV infection
Ongoing risk of reverse seroconversion
Referral to Infectious Diseases Unit advised
Measure HBV viral load, complete workup*

If HBsAb positive ≥ 10 IU/ml
Highly immunosuppressive Regimens
eg. Allogeneic transplant, autologous transplant, AML chemotherapy, Rituximab, Alemtuzumab

HBV prophylaxis OR
if HBsAb > 100 IU/ml
Close monitoring with LFTs, HBsAb, HVB viral load at least 3 monthly
Predictors of reactivation: rising HBV DNA or declining HBsAb
Worsening ALT/AST a later feature. Consider antiviral treatment early

Commence HBV prophylaxis
Entecavir > 1 week prior to chemotherapy
Lamivudine is an alternate agent if < 12 cycles of treatment planned and no cirrhosis present

If HBsAb negative < 10 IU/ml
Highly immunosuppressive Regimens
eg. Allogeneic transplant, autologous transplant, AML chemotherapy, Rituximab, Alemtuzumab

Continue HBV prophylaxis for 6 to 12 months post completion of immuno-suppressive therapy
Specific scenarios related to Allogeneic HSCT donor and recipients

- HBV can be transmitted from previously infected donors
- The decision to use donors with markers of HBV infection must be balanced against the haematological consequences of the patients not receiving a transplant
- Of note, clearance of HBV infection in the HBsAg(+) recipient may occur after transplant from an HBsAb (+) donor, especially if donor infection was acquired naturally (i.e. the donor is both anti HBc and HBsAb positive). Although not usually possible donors with this profile are preferred. HBV vaccination of a HBV naïve donor is probably insufficient to effect viral clearance in an HBV infected recipient.

1. **Recipient with HBsAg -, Anti HBcAb +, anti HBsAb +:**
   - If the donor is HBV marker naïve, these patients can undergo seroconversion and become HBsAg positive post allo HSCT
   - They should therefore be monitored with 3 monthly anti HBsAb levels and if these fall to <10 IU/ml they should receive prophylaxis with entecavir 0.5mg/daily.
   - If HBsAb levels are not present (<10 IU/ml), recipients should be given prophylaxis with entecavir as above.

2. **Donor HBsAg or HBV DNA positive with HBV-naïve recipient:**
   - If donor HBV DNA detected, treat with entecavir or tenofovir until HBV DNA undetectable if feasible
   - Reduce harvest volume to minimum possible and test for HBV DNA
   - Give HB immunoglobulin (HBIG)(0.6 ml/kg or 400 IU IM) immediately prior to infusion of stem cells and consider second dose after 4 weeks
   - Give entecavir to the recipient for a minimum of 12 months post transplant. A longer duration maybe require in the setting of ongoing immunosuppression
   - Monitor HBV DNA, HBsAg and LFTs monthly for 12 months

3. **Donor HBsAg negative, anti HBc positive, with HBV-naïve recipient:**
   - Data from renal transplants suggests HBV can be transmitted in this setting although at a significant lower level than from HBsAg positive donors
   - Management as for HBsAg positive donor as above
References
11. Huang He, Li Xue Ying, Li HR, et al. Preventing hepatitis B reactivation in HBsAg-positive patients with untreated diffuse large B-cell lymphoma with R-CHOP chemotherapy: A prospective study to compare entecavir and lamivudine. J Clin Oncol 31; suppl;abstr 8503