**SUMMARY OF MAIN CHARACTERISTICS OF HEPATITIS B (HBV)**

Hepatitis B is endemic in South Africa, resulting in a significant burden of clinical disease. Patients with chronic HBV infection have a 15 to 40% risk of developing cirrhosis, liver failure or hepatocellular carcinoma (HCC)/liver cancer, and 15 to 25% risk of dying from HBV-related liver diseases.
Risk of chronic infection is dependent on the age of first infection: 70-90% for infants exposed perinatally (from an HBeAg positive mother); 25-50% for children1-5yrs; 6-10% for 5-20yrs and 1-3% for adults >20yrs

***HBV is an entirely vaccine-preventable disease***

**Epidemiology and Transmission in South Africa**

- Estimated 6.9% HBsAg seroprevalence in low risk groups. Up to 25% in HIV infected individuals
- ***Parenteral transmission:*** Main route of transmission is horizontal between ages 6 months to 5 years**.** Other routes of parenteral transmission include perinatal, sexual and percutaneous routes.
- Increased risk of perinatal transmission in HIV/HBV coinfected mothers

**Clinical Presentations**

- ***Acute infection:*** Usually asymptomatic and subclinical in neonates and children. Adolescents and adults usually present with symptomatic hepatitis with/without jaundice
- ***Fulminant hepatitis*** with acute liver failure (0.1% to 0.5%)
- ***Chronic infection*** - **5 different phases of infection.**
  Depending on the phase of infection, the individual maybe completely asymptomatic or present with a hepatitis flare or complications of cirrhosis including jaundice, portal hypertension (varices and ascites) and hepatocellular carcinoma. Hepatocellular carcinoma can occur in the absence of cirrhosis
- **Extrahepatic manifestations**
  Can occur in both acute and chronic hepatitis B
  - Polyarteritis nodosa
  - Membranous glomerulonephritis
  - Membranoproliferative glomerulonephritis

**Diagnosis**

- Depends on combination of ALT, HBV serology, HBV DNA levels and non-invasive markers of fibrosis.
- Liver biopsy seldom required**.**

| Intepretation of serological markers, HBV DNA and ALT levels | |
|---|---|
| ***Successful vaccination*** | • Positive anti-HBsAb (titre >10 IU/ml) |
| ***Previous exposure to HBV*** | • Positive HB IgG core antibody +/- positive anti-HBsAb |
| ***Acute Hepatitis B*** | • HBsAg positive, HB IgM core antibody positive<br>• Elevated ALT |
| ***Fulminant hepatitis*** | • Maybe HBsAg negative, but HB IgM core antibody positive<br>• HBV DNA detectable<br>• Elevated ALT<br>• Synthetic dysfunction (elevated ammonia & prolonged INR>1.5) |
| **Chronic hepatitis B**<br>**ALT, serology and HBV DNA levels depend on phase of chronic infection** | |
| ***HBeAg-positive chronic HBV infection (Immune tolerant)*** | • HBsAg positive, HBeAg positive<br>• High HBV DNA (usually >200 000 IU/ml, typically >1M IU/ml)<br>• Normal ALT |
| ***HBeAg-positive chronic hepatitis (Immune clearance)*** | • HBsAg positive, HBeAg positive<br>• HBV DNA >20 000 IU/ml<br>• Elevated ALT |
| ***HB-eAg negative chronic HBV infection (Immune control)*** | • HBsAg positive, HBeAg negative<br>• HBV DNA <2 000 IU/ml<br>• Normal ALT |
| ***HB-eAg negative chronic hepatitis (Immune escape)*** | • HBsAg positive, HBeAg negative<br>• Hepatitis B IgM core antibody maybe low positive with a flare<br>• HBV DNA >2 000 IU/ml<br>• Fluctuating elevated ALT |
| ***Occult HBV infection*** | • HBsAg negative, anti-HBsAb negative,<br>• Hepatitis B IgG core antibody positive<br>• HBV DNA <200 IU/ ml<br>• Normal ALT |

**Assessment of liver disease and need for therapy**

- Establish phase of chronic infection
- Detailed clinical history and physical examination
- Assessment of the severity of the liver disease
    - Liver profile: total bilirubin, conjugated bilirubin, ALT, AST, ALP, GGT
    - FBC including a differential count
    - Albumin and INR to assess synthetic function
- Look for other co-factors
    - Viral co-infection: HIV, HCV, HDV

- Alcohol
- Non-alcoholic fatty liver disease
- Iron overload
- Drug/toxin-induced liver injury

- Serological assessment
  - HBsAg, anti-HBs, HBeAg and anti-HBe ± HB IgM Ab (note – can be low positive with a flare)
  - Hepatitis B IgG core antibody (if assessing for occult HBV or previous cleared infection)
  - Anti-HAV IgG to assess need for HAV vaccination
- Alpha-fetoprotein
- Ultrasound of the liver and dopplers
- Non-invasive markers of fibrosis
  - APRI Score = (AST/ULN) x 100) / platelet count ($10^9$/L)

    ***APRI Score >2 identifies adults with cirrhosis (F4) and in need of antiviral therapy***
  - Vibration Controlled Transient Elastography (Fibroscan$^R$)
- Liver biopsy-no longer routinely required
  - Excluding other contributing forms of acute/chronic liver disease eg. Drug or toxin-induced liver injury

**Goals of Therapy**

- ***Prevention of long-term complications of chronic hepatitis B***
  - Cirrhosis
  - Liver failure
  - Hepatocellular carcinoma
- ***Prevention of reactivation in setting of immunosuppression/ biologicals/chemotherapy***
- ***Ensure HBV viral suppression in ALF***

***Ideal endpoint of treatment:*** Immunological cure with sustained HBV DNA suppression and sustained HBsAg loss, with/without seroconversion to anti-HBs. Virological cure not yet possible.

**Indications for treatment**

| Patients requiring treatment | Monitoring required |
|---|---|
| • Acute liver failure<br>• Compensated or decompensated cirrhosis (APRI score >2 in adults)<br>  ○ Regardless of ALT levels, HBeAg status or HBV DNA levels<br>• Patients receiving chemotherapy, rituximab or immunosuppressive therapy<br>• HBeAg-positive chronic hepatitis B (Immune clearance )<br>• HBeAg-negative chronic hepatitis B (Immune escape) | • HB-eAg negative chronic HBV infection (Immune control)<br>• HB-eAg positive chronic HBV infection (Immune tolerance) |

**Treatment Options**

- ***Nucleos(t)ide analogue therapy (NUCs):*** Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), entecavir and lamivudine,
- ***Interferon-based therapy:*** Pegylated Interferon – only under the supervision of a hepatologist

**Tenofovir is the preferred NUC.** TAF and entecavir is reserved for patients with renal impairment. Lamivudine should not routinely be used because of high rate of resistance.

**Treatment of Special Populations**

**Pregnancy (See prevention of mother-to-child transmission)**

- **HBsAg screening of pregnant women is essential**
- Indications for therapy: same as usual indications

**HBV/HCV Co-infection**

- Treat Hepatitis B before treating hepatitis C

**HIV/HBV Co-infection**

- All should be treated with an ARV regimen that includes Tenofovir and lamivudine or emtricitabine

**Healthcare workers**

- HBV DNA level should preferably be undetectable or <200 IU/ml before practicing exposure-prone procedures

**Prevention**

***HBV vaccination***

- **Recommend HBV birth dose as part of EPI to prevent perinatal transmission**
- Ideally all South Africans should be vaccinated
- **High risk groups must be vaccinated**
    - Health-care workers
    - All laboratory staff working with clinical specimens
    - Policemen, firemen and members of the armed forces
    - Persons with end stage renal disease requiring dialysis
    - Persons who inject or use drugs
    - Household contacts of HBsAg positive persons
    - Sex partners of HBsAg positive persons
    - Residents and staff of facilities for the developmentally disabled
    - Patients receiving frequent transfusions of blood or blood components
    - Transplant candidates before transplantation
    - Persons seeking evaluation for treatment of a sexually transmitted disease
    - Men who have sex with men
    - Persons with chronic liver disease
    - Persons with HIV infection
    - Personnel and residents of correctional service facilities

***Post-exposure prophylaxis: Needle stick/sexual exposure/percutaneous exposure***

- Wounds washed with soap and water
- Mucous membranes flushed with water
- **Source individual screened:** HBsAg, HIV and anti-HCV
- **Exposed individual screened:** HBsAg, HBsAb and HB IgG core Ab
  - Infected, immune or non-immune
- **Source individual HBsAg positive or status unknown and exposed individual non-immune**
  - HBIG (0.06ml/kg or 500IU) IMI and active vaccination (0,1 and 2 months)
  - Consider repeat HBIG at 1 month
    ~ if contact HBeAg positive or high DNA levels
    ~ if exposed individual known non-responder

***Prevention of MTCT***

- **Pregnant women:** Tenofovir if HBV DNA >200 000 IU/ml, starting at 28-32 weeks gestation
- **Neonate:** HBV birth dose vaccine and HBIG at different sites within 12-24 hours of delivery
  Complete EPI HBV vaccine schedule at 6,10 and 14 weeks

**Diagnostic, Prevention and Treatment Options at Primary, Secondary & Tertiary Levels of Care**

***Diagnosis***

- Viral serology (HBsAg, anti-HBs, HBeAg, anti-HBe, IgG and IgM anti-HB core at all levels of care)
- HBV DNA quantification at secondary and tertiary levels of care

***Assessment of clinical severity***

- Liver profile and INR at all levels of care; enables APRI scoring to assess for cirrhosis
- Ultrasound liver : Secondary and tertiary levels of care
- Fibroscan and Liver biopsy: Tertiary levels of care

***Treatment:***

| **Acute Hepatitis B** | |
|---|---|
| ***Uncomplicated cases*** | • Manage at primary care level<br>• Screen at 6 months to exclude progression to chronic hepatitis B |
| ***Complicated cases with synthetic dysfunction*** | • Refer to Secondary care level |
| ***Fulminant hepatitis*** | • Refer to tertiary care level |
| **Chronic hepatitis B** | |
| ***HBeAg-positive chronic HBV infection (Immune tolerant)*** | • Follow up at primary care level |
| ***HBeAg-positive chronic hepatitis (Immune clearance)*** | • Secondary level care if uncomplicated wth with option of down-referral to primary level care when stable on therapy |

| | |
|---|---|
| | • Tertiary level care if complicated with option of down-referral to secondary level care when stable on therapy |
| ***HB-eAg negative chronic HBV infection (Immune control)*** | • Follow up at primary care level |
| ***HB-eAg negative chronic hepatitis (Immune escape)*** | • Secondary level care if uncomplicated wth with option of down-referral to primary level care when stable on therapy<br>• Tertiary level care if complicated with option of down-referral to secondary level care when stable on therapy |
| ***Cirrhotics (compensated and Decompensated)*** | • Tertiary level care and followup |
| **HIV/HBV, HBV/HCV and HBV/HCV/HIV *Co-infections*** | • Tertiary level care with option of down-referral to secondary or primary level care when stable on therapy |

**Therapeutic Options**

- Lamivudine and TDF : at all levels of care for both HBV mono-infected and HBV/HIV co-infected
- Entecavir,TAF and Pegylated interferon at Tertiary care level

**Prophylaxis**

- Hepatitis B vaccination: all levels of care
- HBIG: all levels of care