THE NORTHERN HOSPITAL

HEPATITIS B

"The Prick of the Needle", oil on canvas, Louis Coulin, 1853.

With fingers weary and worn,
With eyelids heavy and red,
A woman sat, in unwomanly rags,
Plying her needle and thread
Stitch! stitch! stitch!
In poverty, hunger, and dirt,
And still with a voice of dolorous pitch
She sang the "Song of the Shirt."

Work! work! work!
While the cock is crowing aloof!
And work work work,
Till the stars shine through the roof!
It's Oh! to be a slave
Along with the barbarous Turk,
Where woman has never a soul to save,
If this is Christian work!

Work work work
Till the brain begins to swim;
Work work work
Till the eyes are heavy and dim!
Seam, and gusset, and band,
Band, and gusset, and seam,
Till over the buttons I fall asleep,
And sew them on in a dream!

Oh, Men, with Sisters dear!
Oh, Men, with Mothers and Wives!
It is not linen you're wearing out,
But human creatures' lives!
Stitch stitch stitch,
In poverty, hunger, and dirt,
Sewing at once with a double thread,
A Shroud as well as a Shirt.

But why do I talk of Death?
That Phantom of grisly bone,
I hardly fear its terrible shape,
It seems so like my own
It seems so like my own,
Because of the fasts I keep;
Oh, God! that bread should be so dear,
And flesh and blood so cheap!

Work work work!
My Labour never flags;
And what are its wages? A bed of straw,
A crust of bread and rags.
That shatter'd roof and this naked floor
A table a broken chair
And a wall so blank, my shadow I thank
For sometimes falling there!

Work work work!
From weary chime to chime,
Work work work!
As prisoners work for crime!
Band, and gusset, and seam,
Seam, and gusset, and band,
Till the heart is sick, and the brain benumb'd,
As well as the weary hand.

Work work work,
In the dull December light,
And work work work,
When the weather is warm and bright
While underneath the eaves
The brooding swallows cling
As if to show me their sunny backs
And twit me with the spring.

Oh! but to breathe the breath
Of the cowslip and primrose sweet
With the sky above my head,
And the grass beneath my feet
For only one short hour
To feel as I used to feel,
Before I knew the woes of want
And the walk that costs a meal!

Oh! but for one short hour!
A respite however brief!
No blessed leisure for Love or Hope,
But only time for Grief!
A little weeping would ease my heart,
But in their briny bed
My tears must stop, for every drop
Hinders needle and thread!"

With fingers weary and worn,
With eyelids heavy and red,
A woman sat in unwomanly rags,
Plying her needle and thread
Stitch! stitch! stitch!
In poverty, hunger, and dirt,
And still with a voice of dolorous pitch,
Would that its tone could reach the Rich!
She sang this "Song of the Shirt!"

"The Song of the Shirt", Thomas Hood, 1843

In the Emergency Department we may all relate to the lamentations and despair of the Eighteenth century seamstress who is forced to work endless and thankless hours into the night for a pittance, just as "prisoners work for crime" and wishing for every moment just to feel the sky above her head and the grass beneath her feet, even if only for one hour. It is no wonder she is inclined to prick herself with the needle from time to time, especially when tired and momentarily distracted by a handsome colleague as in Coulin's work of 1853.

In the 21st century Emergency Department, there are many parallels with the sweatshop conditions of the Eighteenth century seamstress. Unless we are ever vigilant a needle stick injury is never far away. Whilst the close attention of an attractive college provides the "swooning" seamstress with some compensation in Coulin's work, alas for ourselves all we will get is the additional stress of the possibility of the transmission of a nasty viral disease! Despite the long and the stressful hours therefore, we must nonetheless be ever vigilant.

Portrait of Madame Adelaide Pastoret, oil on canvas, c.1791 - 92, Jacques Louis David. Art Institute of Chicago.

HEPATITIS B

Introduction

Hepatitis B is an acute viral infection of the liver.

It may progress to a **chronic** or **carrier stage** and result in significant long term morbidity and mortality.

Hepatitis B is a vaccine preventable disease.

Post exposure prophylaxis can be undertaken

Specific antiviral agents are available for those infected.

Hepatitis B a *very* significant global health problem.

Terminology [2]

Hepatitis B Surface Antigen (HBsAg):

- A protein on the surface of hepatitis B virus.

  It can be detected in high levels in serum during **acute *or* chronic** hepatitis B virus infection.

  The presence of HBsAg indicates that the person is infectious.

  The body normally produces antibodies to HBsAg as part of the normal immune response to infection.

  HBsAg is the antigen used to make **hepatitis B vaccine**.

Hepatitis B Surface Antibody (anti-HBs):

- The presence of anti-HBs is generally interpreted as indicating **recovery** and **immunity** from hepatitis B virus infection.

  Anti-HBs also develops in a person who has been successfully **vaccinated** against hepatitis B.

Total Hepatitis B Core Antibody (anti-HBc):

- Appears at the onset of symptoms in acute hepatitis B and persists for **life**.

  The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.

IgM Antibody to Hepatitis B Core Antigen (IgM anti-HBc):

- Positivity indicates recent infection with hepatitis B virus (< 6 months).

  Its presence indicates acute infection.

History

The earliest Hepatitis B epidemic on record is by Lurman in 1885.

In 1883 an outbreak of smallpox occurred in Bremen and 1,289 shipyard employees were vaccinated with lymph from other people.

Up to eight months later, 191 of the vaccinated workers became ill with jaundice and were diagnosed as suffering from a "serum hepatitis". Other employees who had been inoculated with different batches of lymph remained healthy.

Lurman's paper, today is regarded as a classic epidemiological study. It proved that contaminated lymph was the source of the outbreak.

The hepatitis B virus itself was discovered until 1966 by the American geneticist **Baruch Blumberg**, (1925 - 2011) at the National Institutes of Health (NIH). He discovered the "Australia antigen" (later known as hepatitis B surface antigen, or HBsAg) in the blood of some indigenous Australians. He later developed diagnostic tests for hepatitis B and a vaccine.

Blumberg was a co-recipient of the 1976 Nobel Prize in Physiology or Medicine (with **Daniel Carleton Gajdusek**), for his work on the hepatitis B virus.

The genome of the virus was sequenced in the early 1980s and the first vaccines soon followed.

Lamivudine was the first nucleoside analogue licensed for HBV (it is also active against HIV polymerase).

Epidemiology

The prevalence of chronic HBV infection in Australia is around 0.5 - 1% of adults.

In Australia, most patients with chronic hepatitis B are migrants from regions with a high prevalence of HBV infection (e.g. Asia, Africa, Mediterranean countries, Pacific Island Nations). Infection is usually acquired in the perinatal period or first few years of life.

The prevalence in Aboriginal and Torres Strait Islander populations is much higher. Depending on the exact region it ranges from 4% up to 26%, (the highest incidence in the world).

In the global scale, HBV is a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma.

An estimated (in 2017) 2 billion people have been infected with HBV worldwide, 350 million of whom have chronic infection

Each year, an estimated 1 million people die as a result of HBV infections, and more than 4 million new acute clinical cases occur.

In countries with low endemicity (HBsAg prevalence < 2 %), most infections occur in young adults, especially among people who belong to known **high-risk groups**.

In higher endemicity areas (HBsAg prevalence ≥2 %), most infections occur as a result of perinatal transmission from HBsAg-positive mothers or early horizontal transmission via close contact in the household family setting.

See also Appendix 1 below.

Pathology

Organism

- The Hepatitis B virus (HBV), is a small partially double-stranded DNA virus.

  It is classified within the of the family of the Hepadnaviridae.

- The outer surface of the virus is glycolipid, which contains the hepatitis B surface antigen (HBsAg).

  Other important antigenic components are the hepatitis B core antigen (HBcAg) and hepatitis B e antigen (HBeAg).

  HBcAg is not detectable in serum, but can be detected in liver tissue in persons with acute or chronic hepatitis B infection.

  HBeAg, and antibodies against HBeAg (anti-HBe) or the HBcAg (anti-HBc), are serological markers of HBV infection.

Reservoir

- The natural reservoir for the hepatitis B virus in humans.

Transmission

Although hepatitis B surface antigen (HBsAg) has been found in *virtually all* body fluids, only the following 3 fluids have been found to be definitely infectious:

- Blood (serum or plasma).

- Semen
- Vaginal fluids.

Relative concentrations of Hepatitis B Virus in various body fluids are as follows:

High	**Moderate**	**Low/not detectable** *(Negligible risk)*
Blood Serum Wound exudates	Semen Vaginal fluid Saliva, (*Salivary transmission is very rare and is thought to occur through human bite exposures only where blood is present*).	Breast milk Tears Sweat Urine Feces

Transmission occurs via **percutaneous** and **per-mucosal** exposure to contaminated blood and body fluids. HBV is 50 - 100 times more infectious than HIV.

This may occur during:

- Sexual contact
- Birth
- Injecting drug use
- Some household activities such as sharing razors or toothbrushes
- Invasive procedures in the community such as tattooing or body-piercing, if there has been inadequate infection control
- Invasive medical or dental procedures if there has been inadequate infection control.
- Hospital acquired needle stick injuries or mucosal surface body fluid exposures. Direct inoculation with fresh blood carries an approximately 30% risk of transmission of Hepatitis B (if not immune). [5]

All **blood** and **blood products** produced for medical purposes in Australia are carefully screened for HBV and other blood-borne viruses using nucleic acid testing.

Incubation Period

- The incubation period ranges from 45 - 180 days, (i.e up to 6 months).

  The average of period is around 60 - 90 days (i.e 3 - 4 months).

Period of communicability

- Transmission by infected people can occur:
  - ♥ Many weeks before the onset of symptoms
  - ♥ Throughout the acute clinical course of the disease
  - ♥ During the chronic state.
- All people who are **HBsAg positive** are potentially infectious.
- Those with **detectable HBV DNA** are **highly** infectious (especially if HBsAg positive).
- The HBV can survive outside the body for up to 7 days.

Susceptibility & resistance

- All non-immune people are susceptible to infection.
- It is thought that lifelong immunity is conferred via acute infection in those who do not become chronically infected.

  However, recent evidence suggests that, in spite of serological recovery (production of anti-HBc and anti-HBs antibodies), there can be *persistence* of the HBV after acute infection.

  Maintenance of the T-cell response is responsible for keeping the virus under control.

  However, reactivation or "flare" can occur in the setting of **immunosuppression** (particularly at the time of withdrawal of immunosuppressive therapy) or other liver injury (for example, alcohol, drugs, other hepatitis viruses).

Clinical Features

ACUTE HEPATITIS B

The spectrum of clinical severity is wide-ranging:

- About 30% of persons have subclinical infections, i.e have *no signs or symptoms.* These cases are detected only after investigation of abnormal liver function tests.

  Asymptomatic cases are more common in children than in adults.

- A small number of cases have an acute fulminating course which can be fatal.

  - ♥ Fulminant and fatal infection occurs more commonly than it does in Hepatitis A, however is still very uncommon overall, (around 1% of acute cases)

    Fatality rates are higher in those > 40 years of age.

- Hepatitis D coinfection:

  - ♥ Hepatitis D coinfection occurs in a small number of patients with hepatitis B infection.

Clinical features are usually similar to those of Hepatitis A, but often are somewhat more severe in relative terms.

Typical cases show the following:

1. Non-specific constitutional symptoms:

   There is insidious onset of:

   - GIT symptoms: nausea, vomiting and anorexia.
   - Lethargy / malaise
   - Myalgias
   - Headache.

2. Abdominal discomfort:

   - Typically, right upper quadrant pain and tenderness.

3. Immune complex features:

   These are occasionally seen and may include:

   - Rashes
   - Arthralgias / arthritis

4. Jaundice

- This appears in about 30 - 50% of cases.

  In children it is seen less commonly (< 10% of cases).

- Dark urine a lighter stools may also be seen

Natural History:

Clinical illness can be protracted, lasting several months.

Around 95 % of immunocompetent adults acutely infected with HBV clear the virus and become hepatitis B surface antigen (HBsAg) negative and hepatitis B surface antibody (anti-HBs) positive within **6 months.**

Some cases become chronic "carriers" and are at risk of long term sequelae.

A percentage will become chronic carriers. The risk of becoming a chronic carrier appears to be age related, chronic infection occurs in: [3]

- 90% of infants infected at birth
- 30% of children infected at age 1 - 5 years
- 6% of persons infected after age 5 years

Chronic *carriers* and are at risk of long terms sequelae, including,

- Chronic active hepatitis.
- Cirrhosis of the liver.
- Hepatocellular carcinoma, (hepatitis B is the commonest cause of this malignancy)

CHRONIC HEPATITIS B [5]

Up to 5 % of immunocompetent adults acutely infected with HBV, will become chronically infected, (and so "carriers").

Chronic hepatitis B is defined as persistent detection of **hepatitis B surface antigen** (HBsAg) for **> 6 months**.

Chronic infection is more common in those with immunodeficiency.

Premature death secondary to cirrhosis / hepatocellular carcinoma (HCC) occurs in 15 - 20 %. of chronically infected persons.

The risk of HCC remains elevated lifelong, even in patients who do not develop cirrhosis.

All patients who are HBsAg positive should be fully assessed to determine the stage of their disease, and regularly reassessed over the course of their infection, because the natural history of chronic hepatitis B determines the optimal timing of treatment.

There are 4 Phases of Chronic Hepatitis B infection as follows:

1. Immune tolerance:
    - High HBV DNA
    - Normal LFTs
    - HBeAg Positive
2. Immune clearance:
    - High HBV DNA
    - Abnormal LFTs
    - HBeAg Positive

    Patients in this group are at risk of progression to cirrhosis and hepatocellular carcinoma.
3. Immune control:
    - Low HBV DNA
    - Normal LFTs
    - HBeAg Positive
    - Anti HBe Positive
4. Immune escape:
    - High HBV DNA
    - Abnormal LFTs
    - HBeAg Negative
    - Anti HBe Positive

See also Appendix 2 below

In the **immune clearance phase** (**phase 2**), patients may spontaneously seroconvert from hepatitis Be antigen (HBeAg) positive to HBeAg negative disease with development of antibodies to HBeAg (anti-HBe).

- Spontaneous seroconversion before the age of 30 years confers a favourable long-term prognosis.

  However, if the immune clearance phase is prolonged, hepatic fibrosis and cirrhosis may develop.

Some patients progress to **the immune escape phase** (**phase 4**), with HBeAg negative disease and increased HBV DNA (more than 2000 IU/mL).

- Such patients are at a high risk of progression to cirrhosis, hepatic decompensation and hepatocellular carcinoma.

  Patients in the immune escape phase can transmit disease to others because they have circulating HBV DNA

  Infectivity relates to viral load (HBV DNA), not HBeAg status.

Investigations

1. FBE
2. CRP
3. U&Es/ glucose
4. LFTs
5. Coagulation profile
6. Hepatitis B PCR (in blood)
7. Co-infection:

   Screening for other **blood borne** or **sexually acquired infections** should also be undertaken, as appropriate.

   - HIV serology
   - Hepatitis A serology
   - Hepatitis C serology

- Hepatitis D serology

8. Hepatitis B Serology:

   - HBV infection is confirmed by the detection of hepatitis B surface antigen (HBsAg) or HBV DNA in serum.

     Serology tests further determines whether infections are newly acquired or reflect chronic carriage.

TEST	**RESULT**	**INTERPRETATION**
HepB S-Ag **Anti- HepB-c** **Anti-HepB-s**	NEGATIVE NEGATIVE NEGATIVE	**Susceptible, will need vaccination.**
HepB S-Ag **Anti- HepB-c** **Anti-HepB-s**	NEGATIVE POSITIVE POSITIVE	**Immune due to previous (i.e natural) infection**
HepB S-Ag **Anti- HepB-c** **Anti-HepB-s**	NEGATIVE NEGATIVE POSITIVE	**Immune due to hepatitis B vaccination.**
HepB S-Ag **Anti-HepB-c** **IgM anti-HepB-c** **Anti-HepB-s**	POSITIVE POSITIVE POSITIVE NEGATIVE	**Acutely Infected**

HepB S-Ag **Anti-HepB-c** **IgM anti-HepB-c** **Anti-HepB-s**	POSITIVE POSITIVE NEGATIVE NEGATIVE	**Chronic carrier**
Hb S-Ag **Anti-HepB-c** **Anti-HepB-s**	NEGATIVE POSITIVE NEGATIVE	**Here there are five possible interpretations:** ● May be recovering from acute HBV infection ● May be distantly immune and test not sensitive enough to detect very low level of anti-HBs in serum ● May be susceptible with a false positive anti-HepB-c ● May be undetectable level of HepB s-Ag present in the serum and the person is actually a chronic carrier ● Maternal antibody.

See also Appendix 3 below for time frames for acute and chronic serology patterns

Management

Prevention:

Vaccination:

Hepatitis B vaccines are prepared using recombinant technology.

Hepatitis B vaccination is a part of the Australian national childhood immunization program.

There are a number of vaccination regimes used.

For full vaccination details, see the "The Australian Immunization Handbook".

In **general** terms:

1. From **birth** children receive 4 doses at:

- Birth, an initial dose of hepatitis B virus vaccine is given at birth, before leaving hospital.
- 2 months
- 4 months
- 6 months

2. Children and young adults aged < 20 years:

   For older children and young adults aged < 20 years (who have not received hepatitis B vaccination earlier in life) a 3 dose schedule of the **paediatric formulation** (0.5 mL) of monovalent hepatitis B vaccine can be used at times:

   - 0 (i.e day of initial vaccination).
   - 1 month
   - 6 months

3. Adults aged ≥ 20 years:

   For adults, monovalent hepatitis B vaccine **adult formulation** (1.0 mL) is given in a 3 dose schedule at times:

   - 0 (i.e day of initial vaccination).
   - 1 month
   - 6 months

4. **Accelerated** schedules:

   Accelerated schedules, consist of 4 doses in total

   Accelerated schedules should only be used for those persons with an **imminent** risk of exposure, e.g. those intending to travel to hepatitis B endemic areas with a very limited time before departure.

   There are 2 options:

   Accelerated:

   - 1st dose: day 0 (i.e day of vaccination)
   - 2nd dose: 1 month after 1st dose

- 3rd dose: 2 months after 1st dose
- 4th dose: 12 months after 1st dose

Very accelerated:

- 1st dose: day 0 (day of vaccination)
- 2nd dose: 7 days after 1st dose
- 3rd dose: 21 days after 1st dose
- 4th dose: 12 months after 1st dose

As **higher** seroprotective rates after the **3rd** dose of an accelerated 4 dose schedule are seen after the **0, 1, 2, 12 months** schedule than after the **0, 7, 21 days, 12 months** schedule, it is recommended that the **latter** schedule only be used in **exceptional** circumstances.

Non-responders:

Although uncommon, about 5% on average of those who complete the hepatitis B vaccination series may not acquire immunity.

If adequate anti-HBs levels (i.e **≥10 mIU / mL**) are not reached after the third dose:

- If unknown, test to exclude HBV infection (HBsAg and anti-HBc).
- HBsAg negative non responders should be offered further doses:

  These are given as either:

  - ♥ A fourth double dose

  Or

  - ♥ A further 3 doses at monthly intervals, with further testing for response at least 4 weeks after the last dose.

Persistent non-responders should be informed that they are not protected and should minimise exposures. They should be told about the need for **Hepatitis B Immunoglobulin** *within* **72 hours** of parenteral exposure to HBV.

Booster doses:

Booster doses of hepatitis B vaccine (after completion of a primary course using a recommended schedule) are *not* recommended for **immunocompetent** persons.

This applies to children and adults, including healthcare workers and dentists.

This is because there is good evidence that a completed primary course of hepatitis B vaccination provides **long-lasting** protection.

Even though **vaccine-induced** antibody levels may decline with time and may become undetectable, **immune memory** persists and is thought to result in a protective immune response on re-exposure

However, booster doses **are** recommended for persons who are **immunocompromised**, in particular those with either HIV infection or renal failure. The time for boosting in such persons should be decided by regular monitoring of anti-HBs levels at 6 to 12 monthly intervals.

Post exposure prophylaxis

After exposure to Hepatitis B virus (HBV), appropriate and timely prophylaxis can prevent HBV infection and the subsequent risk of development of chronic infection or liver disease.

Post-exposure prophylaxis (PEP) consists of:

1. Hepatitis B vaccine, (in the non-immune)

2. Hepatitis B immune globulin

Blood should be taken, if possible, from the "source" for serology testing.

Blood is taken from the "recipient" for serology testing, (in addition to hepatitis C and HIV serology)

If the recipient's antibody levels are of a protective level, (i.e **≥ 10 mIU / mL**) then no further action is required (with respect to hepatitis B management).

In **general** terms: [4]

Type of exposure	**Hepatitis B Immunoglobulin**	**Vaccine**
Perinatal (exposure of babies during and after birth)	100 IU, by IM injection Single dose immediately after birth (preferably within 12 hours of birth and certainly within 48 hours)	0.5 mL, by IM injection Immediately after birth (preferably within 24 hours, no later than 7 days),† then at 2, 4 and 6 months of age

Percutaneous, ocular or mucous membrane	400 IU, by IM injection *Or* 100 IU, if body weight < 30 kg Single dose within 72 hours of exposure	0.5 mL or 1 mL (depending on age), by IM injection Within 7 days† of exposure and at 1 and 6 months after 1st dose
Sexual	400 IU, by IM injection *Or* 100 IU, if body weight < 30 kg Single dose, preferably within 72 hours of last sexual contact ‡	0.5 mL or 1 mL (depending on age), by IM injection Within 14 days† and at 1 and 6 months after 1st dose

† The 1st dose can be given at the same time as HBIG, **but should be administered at a separate site**. Administration **as soon as possible after exposure** is preferred.

‡ There is limited evidence for efficacy if given within 14 days of contact; however, administration as soon as possible after exposure is preferred.

For full immune prophylaxis details, see the "The Australian Immunization Handbook".

Control of contacts:

Non-immune sexual contacts should be offered hepatitis B immunoglobulin (HBIG) 400 IU IM within **14 days of contact**, and commence the **hepatitis B vaccination program at 0, 1 and 6 months**. This results in protective immunity in approximately 90% of people.

Household contacts should be tested for HBsAg and anti-HBc, and offered vaccination if susceptible.

Infants born to HBsAg-positive mothers should be given a single dose of HBIG and vaccine within 12 hours of birth, at different sites. The remaining doses of vaccine should be given at 2, 4 and 6 months of age, as per the National Immunisation Program schedule.

Recipients of needlestick injuries from an HBV positive source should be considered for hepatitis B immunoglobulin and vaccination if they are HBV negative.

Treatment of Acute Infection:

Oral **antiviral therapy** may improve clinical outcomes in patients with **severe** or **fulminant** hepatitis B. Discussion with a transplant team however is strongly advised before starting any treatment.

Treatment of Chronic Infection:

In general, patients in the **immune clearance** and **immune escape** phases of chronic infection (where LFTs are abnormal) are candidates for therapy.

Factors taken into consideration for treatment include:

1. **Patients with high HBV DNA**.
2. Phase of infection
3. Patient's age
4. Degree of inflammation
5. Fibrosis stage
6. Overall Risk of hepatocellular carcinoma.

All infected patients should be educated regarding transmission routes, safe injecting and sexual practices, blood and body fluid precautions, and not donating organs or blood.

Hepatitis B Anti-viral agents: [6]

It is important to choose an antiviral therapy with a high likelihood of **HBV DNA suppression** and **a low chance of resistance**.

Therefore the **current** first-line therapies for treatment naïve Hepatitis B infected patients are:

Entecavir (ETV):

- ETV is a nucleoside analogue.
- It has excellent tolerability, high potency and a high barrier to resistance (only 1.2% at 6 years in treatment naïve patients).
- It has a higher rate of resistance if used in patients with lamivudine-resistant HBV, therefore avoid ETV in this context.

Tenofovir (TDF):

- TDF is a nucleotide analogue.
- It has high potency and a high barrier to resistance (0% at 3 yrs in treatment-naïve patients).
- TDF retains high activity against lamivudine-resistant HBV and is also active against **HIV**.
- It should be avoided in patients with **renal disease**.
- There is increasing safety in pregnancy data, **so it is the treatment of choice in women with childbearing potential** requiring prolonged antiviral therapy for treatment of chronic hepatitis B..

Pegylated Interferon (PEG-IFN):

- PEG-IFN is less likely to be prescribed because of its adverse **side effects**, but it does have a defined one year duration of therapy with the possibility of HBsAg clearance.
- PEG-IFN can be useful in selected younger patients, particularly women who are intending to get pregnant in the future.
- A response is more likely in HBeAg-positive patients with high ALT and low HBV DNA viral load.

Lamivudine was the first nucleoside analogue licensed for HBV (it is also active against HIV polymerase). It is well tolerated, but has a major problem with regards to resistance. Approximately 70% of patients after 5 years on lamivudine have resistant HBV (YMDD mutation). It also causes **cross-resistance** with entecavir and telbivudine. It is no longer first line therapy in Australia, though it is still used in special circumstances or continued in patients with sustained response over years. For lamivudine resistant patients combination therapy of tenofovir and lamivudine is used.

It is important to encourage treatment adherence to avoid antiviral resistance and risks associated with sudden cessation.

Notification:

Hepatitis B infection (Group B disease) must be notified in writing within 5 days of diagnosis.

This is a Victorian statutory requirement.

School exclusion:

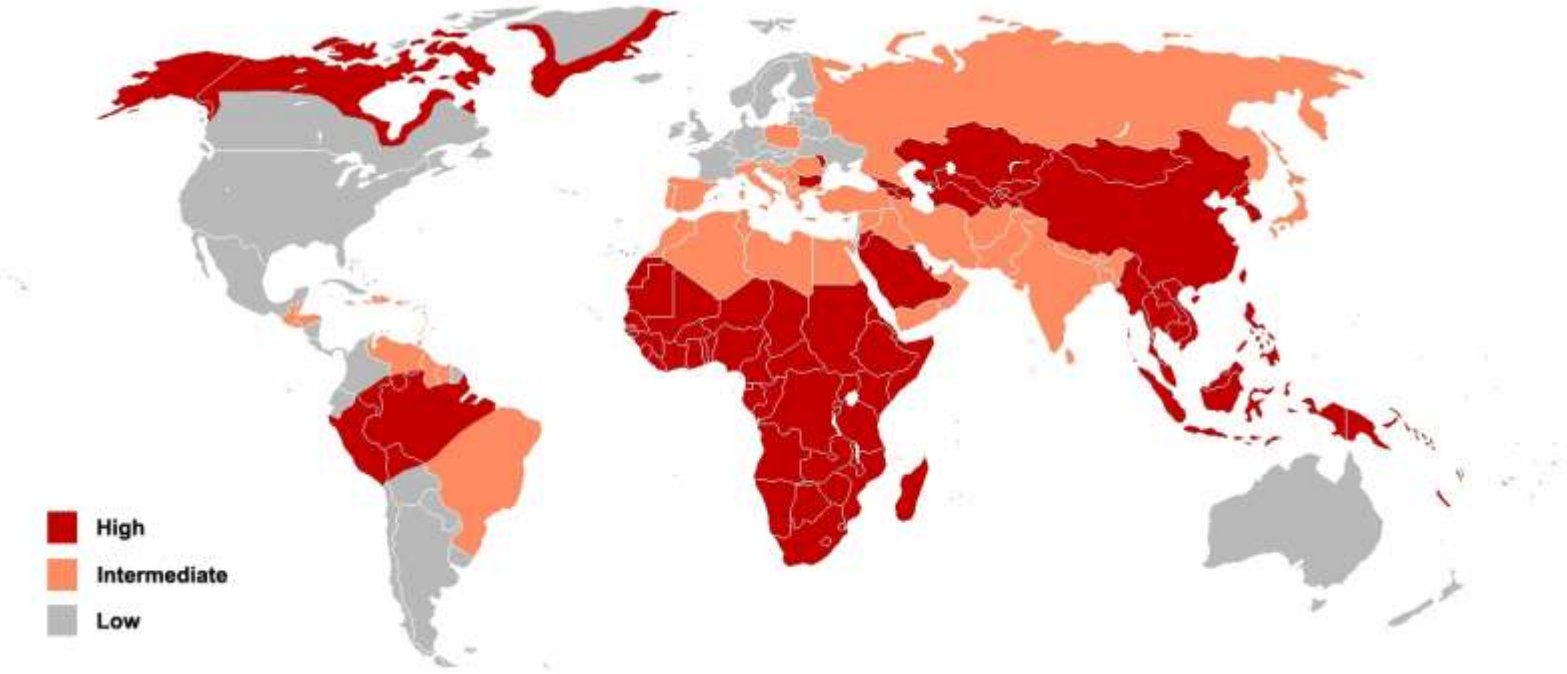
Primary school and children's services centre exclusion for hepatitis B is not applicable.

Disposition:

All infected patients should be referred initially to a gastroenterology or a specialist hepatitis clinic to discuss treatment options and to plan longer term surveillance for cirrhosis/ hepatocellular carcinoma.

Appendix 1

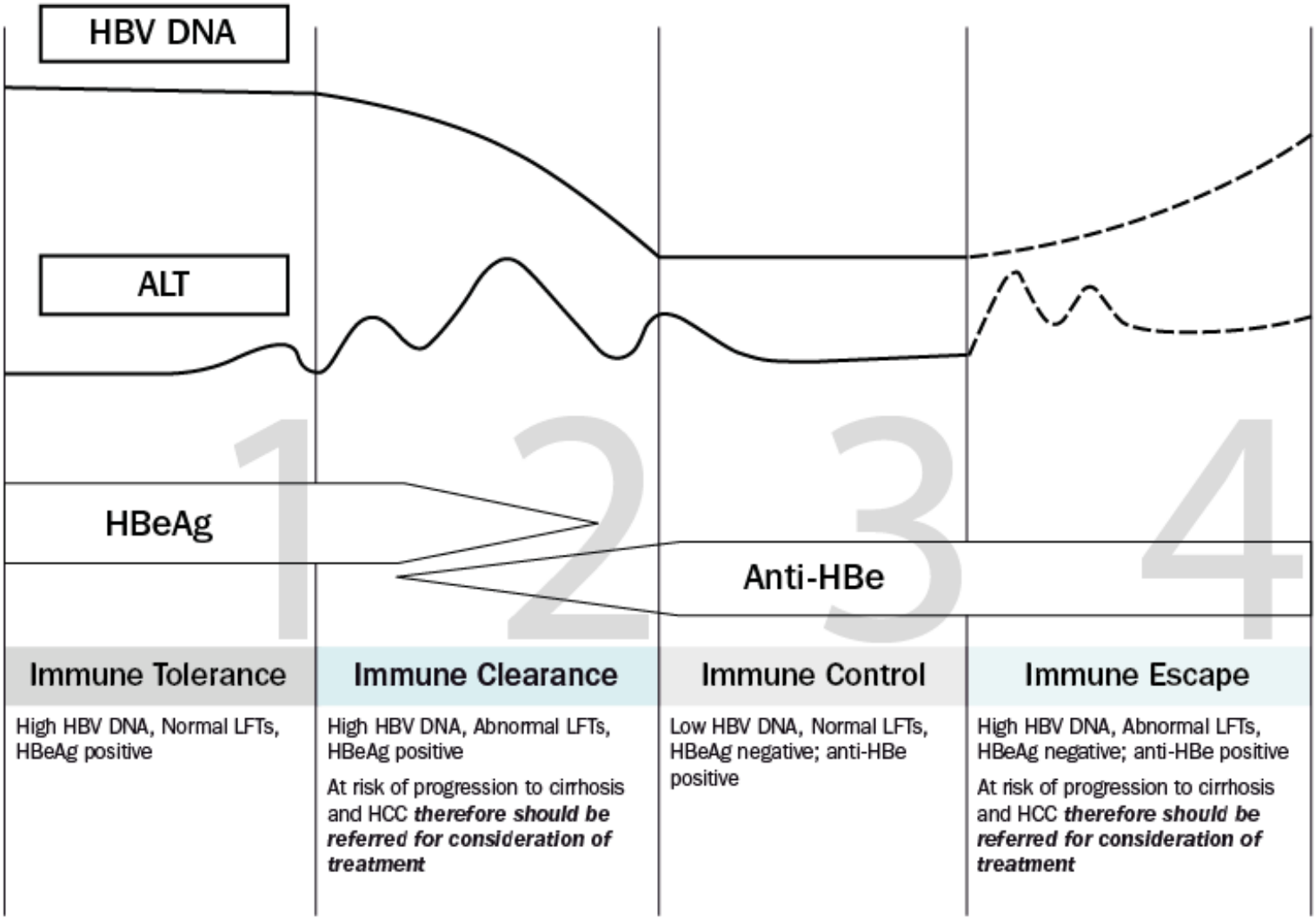
Epidemiology of Hepatitis B:



Global Hepatitis B prevalence, 2005 (CDC)

Appendix 2

The 4 Phases of Chronic Hepatitis B Infection (summary description):



ALT = alanine aminotransferase

Anti-HBe = antibodies to HBeAg

HBeAg = hepatitis B e antigen

HBV = hepatitis B virus

HCC = hepatocellular carcinoma

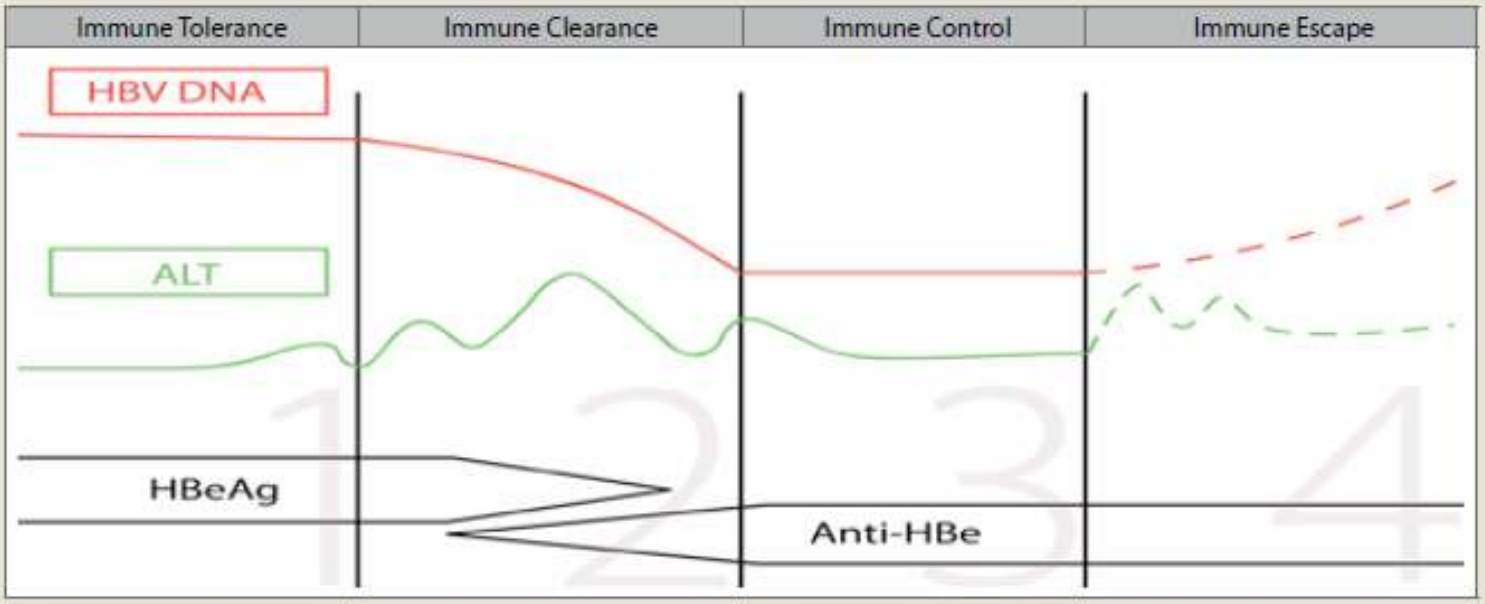
LFTs = liver biochemistry

The 4 Phases of Chronic Hepatitis B Infection (detailed description): [6]

Natural history of CHRONIC hepatitis B virus infection

The four phases of chronic hepatitis B

There are 4 phases, of variable duration, that characterise chronic hepatitis B:[22]

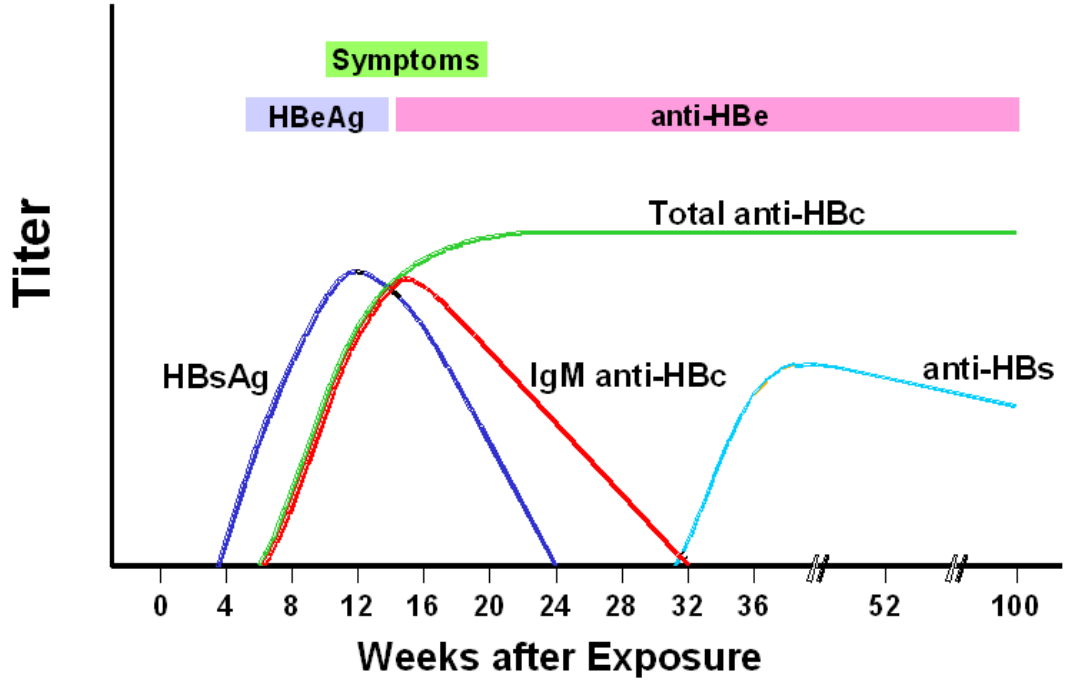


1 Immune Tolerance	2 Immune Clearance	3 Immune Control	4 Immune Escape
This initial phase is characterised by hepatitis B e antigen (HBeAg) positivity, high HBV DNA levels (>20,000 IU/mL), and normal ALT levels. It is prevalent in those who acquired the infection vertically. This phase may persist for decades and is associated with a low risk of progression to advanced liver disease.	The liver injury in HBV is determined by the immune response to the virus. This phase is characterised by fluctuating HBV DNA and ALT levels and HBeAg positivity as an active, immune-mediated cytotoxic response to the infected liver cells. Active inflammation and eventually fibrosis can be found in the liver following these repeated immune-mediated attacks. **At risk of progression to cirrhosis and HCC therefore should be considered for treatment.**	Liver inflammation is minimal, HBV DNA is undetectable or at a low level (<2000 IU/mL) and liver function tests (LFTs) are normal. These patients do not require treatment unless there is advanced liver disease.	This phase is characterised by negative HBeAg, positive anti-HBe and detectable viral load (HBV DNA > 2000 IU/mL). It is often termed precore mutant HBV because a mutation in the precore region of the DNA results in a lack of HBeAg production. Patients can reach this phase from the immune control state (5–10%) or can progress directly from HBeAg-positive chronic hepatitis to HBeAg-negative chronic hepatitis (10–30%). **At risk of progression to cirrhosis and HCC therefore should be considered for treatment.**

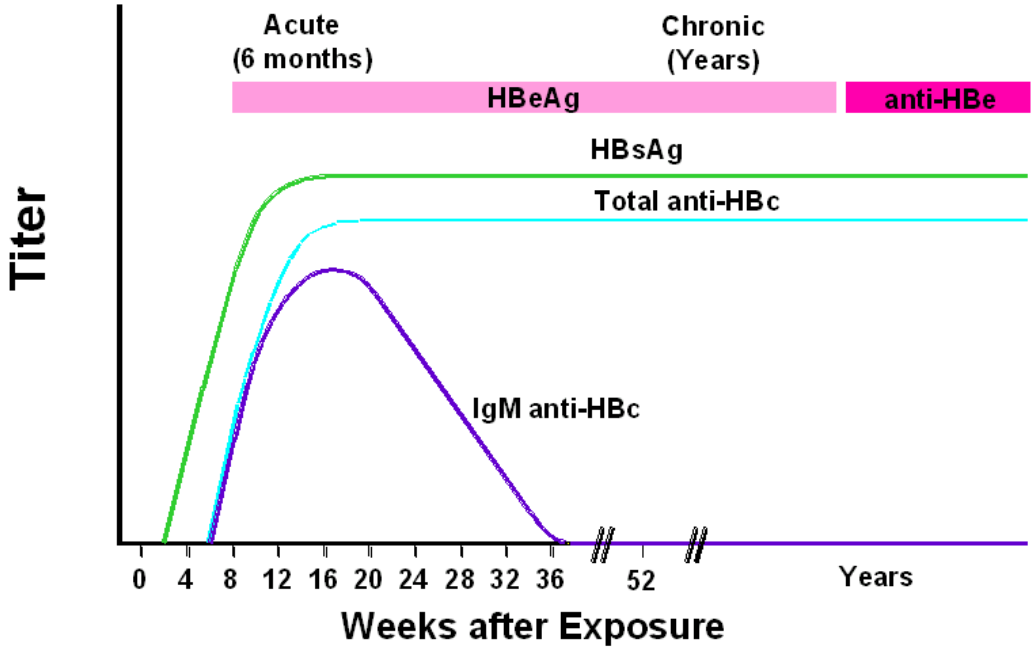
The risk of developing CHB depends on the age of the person when the virus was contracted: **>90% for infant (<5 years)** **~30% during childhood** **<5% of adults**	People with chronic HBV infection usually exhibit **NO SYMPTOMS** until they have developed cirrhosis or liver cancer.	CHB is defined as persistent detection of **HBsAg for >6 months** after initial exposure to the virus. Positive HBsAg in most settings reflects the presence of chronic HBV.	CHB is a **dynamic disease**, patients move between phases. **Patients must be regularly re-evaluated** to determine which phase they are in.

Appendix 3 *Time frames for serology patterns:*

Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course



Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course



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