UNIT NO. 1

CHRONIC HEPATITIS B INFECTION MANAGEMENT

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ABSTRACT

The Chronic Hepatitis B (CHB) infection is considered a life long illness with 3 recognized phases. Long term follow up for disease progression and complications is required. Current treatments for CHB aim to reduce viraemia for as long as possible. The present armamentarium of drugs include interferons and the increasing spectrum of nucleotide and nucleoside analogues. The indications, benefits and limitations of therapy should be understood before starting a regime.

SPECTRUM OF PRESENTATION

The Chronic Hepatitis B (CHB) patient can present in any one of the 3 phases of the Chronic Hepatitis B infection: *immune tolerance, immune active and the inactive carrier phases* (Table 1).

The *immunotolerant phase* is the initial phase after patients acquired HBV infection, typically in the perinatal period. This phase is characterized by normal alanine aminotransferase (ALT), presence of HBe Ag, serum HBV DNA $>10^5$ copies/ml and minimal changes on liver biopsy. The immune tolerant phase usually lasts 10-30 years. The immune tolerant phase is rarely observed or very transient in patients with childhood or adult-acquired HBV infection. Patients are asymptomatic and have no signs of liver dysfunction clinically during this phase of immune tolerance to HBV.

The *immune active phase* is the phase when the immune response to HBV infection becomes more active. Immune mediated events occur during this time, with variable viral clearance. This phase is characterized by active liver disease, marked by raised ALT and necroinflammation on liver biopsy. There is usually high level of serum HBV DNA during this phase. The Hepatitis B e Ag (HBe Ag) can be positive or negative in this phase:

- In Hepatitis B e Ag positive immune active CHB, there may be spontaneous HBe Ag clearance, which could occur at a rate of up to 20% per year.
- The Hepatitis B e Ag negative immune active CHB patients were mostly initially HBeAg positive and had wild type HBV. However, around the time of HBeAg seroconversion, selection of precore and/or core promoter region mutations occurred that led to the downregulation of HBeAg production.

Most of the patients with immune active CHB are asymptomatic and discovered only during routine follow up with blood tests. However, a small percentage develop symptoms like acute hepatitis. The patient with HBeAg negative immune active CHB tends to be older as this occurrence usually represents a later phase in the natural history of chronic HBV infection. These patients can have a fluctuating course, with intermittently elevated ALT and HBV DNA levels.

It is during the immune active phase that the patient is at risk of developing significant liver disease like liver fibrosis due to the necroinflammatory episodes, particularly, if these had repeatedly occurred.

The *inactive carrier* CHB patient has normal ALT and the HBeAg is negative. It is now understood that HBV replication can exist during this phase but levels rarely exceed 10^4 copies/ml. The outcome of these patients depends on the liver damage sustained prior to HBeAg seroconversion and the durability of this inactive carrier state. As mentioned, a proportion can progress to HBeAg negative immune active CHB later.

FOLLOW UP OF CHRONIC HEPATITIS B INFECTION

All patients with Chronic Hepatitis B infection must be followed up life long. The aims of this long term monitoring are 2 fold – to assess indications for antiviral treatment and to evaluate disease progression, including hepatocellular carcinoma (HCC) development.

The general guideline for patients in the immuno-tolerant and inactive phases would be a clinical consultation and an ALT measurement 6 monthly. For patients in the immune active phase and on treatment, the follow up varies with more regular clinical reviews and liver panel tests. Most guidelines on HCC surveillance are targeted for high risk carriers like patients above 40 years, patients with cirrhosis and those with a family history of HCC. Monitoring for HCC is done usually with 6 monthly alphafetoprotein assessment and ultrasound. Prospective data showed that with surveillance, HCC tumours are detected at an earlier stage when treatment options are still viable.

Patients with chronic HBV infection must also be counseled on matters that can potentially decrease the disease progression and to lessen the transmission of infection. These measures include decrease or stop alcohol consumption, decrease or stop smoking, maintain ideal weight, go for Hepatitis A vaccination and practice safe sex. Close contacts of chronic HBV patient should be screened and be vaccinated appropriately.

GOALS AND INDICATIONS FOR TREATMENT

The ideal goal for the patient with chronic HBV infection is to eradicate the virus completely. But at this current time, this is not possible. Hence, the primary aim of treatment for the chronic HBV patient is to suppress the HBV DNA to low or undetectable levels for as long as possible.

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Table 1. Phases of Chronic Hepatitis B infection

Definitions	Diagnostic Criteria
Immune-Tolerant Chronic HBV Infection Persistent HBV infection without immune reaction	o HBsAg-positive > 6 months o Serum HBV DNA > 10^5 copies/mL o Persistently normal ALT levels o Liver biopsy showing normal histolology or minimal non-specific changes
Immune active Chronic Hepatitis B Chronic necroinflammatory liver disease Caused by persistent HBV infection	o HBsAg-positive > 6 months o Serum HBV DNA > 10^5 copies/mL (10^4 copies/mL for HBeAg-negative disease) o Persistent/intermittent ALT elevation o Liver biopsy showing chronic active hepatitis (necroinflammation seen)
Subdivided into: o HBeAg - positive chronic hepatitis B o HBeAg - negative chronic hepatitis B	 o HBeAg - pos, anti-HBe - neg o HBeAg - neg, anti-HBe - pos
Inactive HBsAg Carrier State Persistent HBV infection without virological, or biochemical evidence of active infection	o HBsAg - positive > 6 months History of HBeAg - pos CHB o HBeAg-negative, anti-HBe - positive o Serum HBV DNA < 10^4 copies/mL o Normal ALT levels

The secondary aims of therapy would be to normalize ALT if this is abnormal, achieve HBeAg seroconversion and prevent histological progression. In the cirrhotic patient, aim of treatment would also include preventing disease complications.

The decision to start treatment should take into consideration benefits versus unfavourable factors such as transient sustained response, drug side effects, drug resistance and costs. Guidelines and recommendations for treatment such as the one listed in Table 2 can vary and it is important to recognize that treatment may have to be individualized. Patients should also be educated on the treatment options.

HBV THERAPIES

Current approved treatments for chronic HBV infection can be divided into the nucleoside/nucleotide analogues and the immune modulators. Presently, the United States FDA has approved the use of Lamivudine, Adefovir, Dipivoxil and Entecavir, which are the oral nucleoside and nucleotide analogues, as well as subcutaneous Interferon alfa-2b and Peginterferon alfa-2a, which are the immune modulators. In Singapore, subcutaneous thymosin is also approved. Recently, there has also been studies that demonstrate good safety and efficacy of Peginterferon alfa-2b.

Tables 3-5 list the recommendations for these various HBV therapies in the various clinical settings. It is often not easy to select the most optimal regime. An understanding of the advantages and disadvantages of the major drugs used for chronic HBV infection (Table 6) should be made known to the patient as well.

Table 2. Indications for Antiviral Treatment

ALT (copies/mL)	HBV DNA	Recommendation
HBeAg-positive		
o < 2 x ULN	> 5 $\log_{10}$	No treatment, monitor Treat if: ALT 1-2 x ULN or intermittently elevated, with moderate/severe inflammation or advanced fibrosis on biopsy
o > 2 x ULN	> 5 $\log_{10}$	Observe 3-6 months: treat if no spontaneous HBeAg serconversion Immediate treatment if: decompensated or icteric
HBeAg-negative		
o < 2 x ULN	> 5 $\log_{10}$ > 4 $\log_{10}$	No treatment, monitor Treat if: ALT 1-2 x ULN or HBV DNA 4-5 $\log_{10}$, with moderate/severe inflammation or advanced fibrosis on biopsy
o > 2 x ULN	> 5 $\log_{10}$ > 4 $\log_{10}$	Treatment

ULN = upper limit of normal

Table 3. Recommendations for Treatment of HBeAg-Positive Patients

HBV DNA (copies/mL)	ALT	Treatment Strategy
< 10^5	Normal	o No treatment o Monitor every 6 months
> 10^5	Normal	o Low rate of HBeAg seroconversion for interferon, lamivudine, adefovir, and probably entecavir and peginterferon
> 10^5	Elevated	o Lamivudine, adefovir, entecavir, peginterferon, or interferon are first-line options o If “high” HBV DNA (> 10^7), adefovir, lamivudine, or entecavir preferred

Table 4. Recommendations for Treatment of HBeAg-Negative Patients

HBV DNA (copies/mL)	ALT	Treatment Strategy
$< 10^5$	Normal	o No treatment o Monitor every 6 months
$> 10^5$ $> 10^4$	Normal	o Low efficacy for lamivudine, interferon, adefovir, entecavir o Consider biopsy; treat if disease is active
$> 10^5$ $> 10^4$	Elevated	o Adefovir, lamivudine, entecavir, peginterferon, or interferon are first-line options o Long-term treatment required o Adefovir or entecavir preferred (low rate of resistance)

Table 5. Recommendations for Treatment of Cirrhotic Patients

HBeAg Status	HBV DNA (copies/mL)	Cirrhosis	Treatment Strategy
Positive or negative	$< 10^4$	Compensated	o May treat or observe o Adefovir, lamivudine, or entecavir preferred
Positive or negative	$> 10^4$	Compensated	o Adefovir, lamivudine, or entecavir are first-line options o Long-term treatment required o Adefovir or entecavir preferred (low rate of resistance) o Combination adefovir plus lamivudine has theoretical advantage because of low likelihood of resistance to either drug
Positive or negative	$> 10^4$	Decompensated	o Adefovir or lamivudine, and possibly entecavir, are first-line options o Long-term treatment required o Adefovir and possibly entecavir preferred (low rate of resistance) o Combination therapy may be preferred because of low likelihood of resistance to either drug o wait list for liver transplantation

Table 6. Advantages and Disadvantages of Current Therapies for Chronic Hepatitis B Infection

Agent	Advantages	Disadvantages
Inteferon	o HBsAg loss o Short treatment duration o No resistance	o Parenteral administration o Poor tolerance
Lamivudine	o Oral administration o Excellent tolerance o Use in ESLD o Use in adefovir failures	o Drug resistance common (~20%/yr)
Adefovir	o Oral administration o Excellent tolerance o Use in ESLD o Use in lamivudine failures	o Drug resistance, though uncommon (0% at year 1, ~2% at year 2, 7% at year 3, 15% at year 4)
Entecavir	o Oral administration o Excellent tolerance o Use in lamivudine failures	o Drug resistance uncommon (0% at year 1; resistance mutations noted in previously lamivudine-resistant patients)
Peginterferon	o HBsAg loss o Fixed duration of treatment	o Parenteral administration o Tolerance better than Interferon but less than oral agents

ESLD, end-stage liver disease

REFERENCES FOR FURTHER READING

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3. Liaw YF, Leung N, Guan R, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: An update. J Gastroenterol Hepatol. 2003; 18:239-45.

LEARNING POINTS

- **Chronic Hepatitis B (CHB) infection is considered a life long illness with 3 recognized phases.**
- **The immune tolerant phase is characterized by normal alanine aminotransferase (ALT) , presence of HBe Ag, serum HBV DNA >10^5 copies /ml and minimal changes on liver biopsy.**
- **The immune active phase is characterized by active liver disease, marked by raised ALT and necroinflammation on liver biopsy.**
- **The inactive carrier phase is characterised by has normal ALT and the HBeAg is negative.**
- **All patients with Chronic Hepatitis B infection must be followed up life long.**
- **Patients with chronic HBV infection must also be counseled on matters that can potentially decrease the disease progression and to lessen the transmission of infection.**
- **Current approved treatments for chronic HBV infection can be divided into the nucleoside/nucleotide analogues and the immune modulators.**