The Six Clinical Stages of CHB Infection

<u>HBeAg Positive</u>	
Immune Tolerant	May present up to the third decade of life. Usually asymptomatic, normal ALT values, HBV DNA levels range from 2,000,000 to 200,000,000,000 iu/ml (10^7 – 10^{12} copies/ml). Liver biopsy or elastography findings of minimal or no fibrosis. [a] Little or no progression after 5 years follow-up.[b,c]
Chronic Hepatitis	May present with or without symptoms, elevated ALT values, HBV DNA 20,000 to 20,000,000 iu/ml (10^5 – 10^8 copies/ml). Liver biopsy shows acute necroinflammation and moderate to advances fibrosis.
Cirrhosis	Usually present in forth to fifth decade of life, elevated ALT values, HBV DNA 20,000 to 2,000,000 iu/ml (10^5 – 10^7 copies/ml). May have decreased albumin levels and low platelet counts.
<u>HBeAg Negative</u>	
Low Replication Stage (i.e. inactive carver)	Normal ALT value, HBV DNA ≤ 2000 iu/ml (≤ 10^4 copies/ml). Prognosis good. However, reversion to active liver disease may occur.
Chronic Hepatitis	Characteristics similar to HBeAg positive chronic hepatitis patients.
Cirrhosis	Characteristics similar to HBeAg positive cirrhosis patients.

*Reversion to active liver disease may occur at any stage of HBV infection.

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Supplemental Table 1

Predictions of Progression in CHB patients

HBeAg	Used as a surrogate marker for high levels of serum HBV DNA. HBeAg has been reported to be a risk factor for chronic hepatitis, cirrhosis, and HCC. [a,b,c]
HBV Genotype	Genotype C is predictive of non chemical outcomes and HCC development.[d,e,f,g] Genotype B is associated with HCC in younger Taiwanese patients and in older Japanese patients.
HBV-DNA	A linear relationship between progression to cirrhosis and to development of HCC in Taiwanese[h,i,j]. The rate of progression to cirrhosis increased with increasing levels of HBV DNA starting from 2000 iu/ml (10^4 copies/ml). Also the incidence of HCC increased from 1.3% for HBV DNA < 60 iu/ml (< 300 copies/ml) to 14.9% for HBV DNA levels ≥ 200,000 iu/ml (≥ 10^6 copies/ml)
BCP Mutants	BCP mutants were detected more frequently in HCC patients with high HBV DNA levels and Genotype C. [e,g,k] The BCP mutants was associated with an increased risk for disease progression and development of HCC in both genotypes B and C patients. [e,f]
PC Mutants	PC Mutants are most often detected in HBeAg negative CHB patients. [c,d,e,f,g,i,k,l,m] PC mutants are associated with ALT elevations, increased HBV DNA levels, and persistent hepatic necroinflammation.
AFP	Elevated AFP levels during ALT flares, in the absence of HCC, were detected in CHB patients who progressed to cirrhosis and may be used as a marker for antiviral therpy.

HBeAg: Hepatitis B “e” antigen
HBV: Hepatitis B virus
HBV DNA: Hepatitis B virus deoxyribonucleic acid
BCP: Basal core promoter
PC: Precore
AFP: Alpha-fetoprotein

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Treatments for Hepatocellular Carcinoma

1) Surgery
    a) Resection
    b) Liver Transplantation
2) Interventional Radiology
    a) Percutaneous Ablative Techniques
        1) Ethanol
        2) Radiofrequency
        3) Microwave
        4) Irreversible electroporation
    b) Transcatheter Techniques
        1) Chemoemobolization
        2) Drug eluting beads
        3) Yttrium – 90
3) Oncology
    a) Chemotherapy
    b) Immunotherapy

Supplemental Table 3

Summary of Published Guidelines and Algorithms for Treatment for HBV Infection

	HBeAg Positive			HBeAg Negative			Compensated Cirrhosis		Decompensated Cirrhosis	
	HBV DNA	ALT	Histology	HBV DNA	ALT	Histology	HBV DNA	ALT	HBV DNA	ALT
EASL Guidelines 2017	>2,000 IU/mL	> ULN	Mod G/Mod F	>2,000 IU/mL	> ULN	Mod G/Mod F	Detectable	NA	Detectable	NA
	>2,000 IU/mL	< ULN	Mod G/Mod F	>2,000 IU/mL	< ULN	Mod G/Mod F				
APASL Guidelines 2012	>20,000 IU/mL	> 2x ULN	NA	>2,000 IU/mL	> 2x ULN	NA	>2,000 IU/mL	NA	NA	NA
AASLD Guidelines 2015	>20,000 IU/mL	> 2x ULN	NA	>2,000 IU/mL	> 2x ULN	NA	Detectable	NA	NA	NA
US Algorithm 2015	>2,000 IU/mL	> ULN	NA	>2,000 IU/mL	> ULN	NA	Detectable	NA	Detectable	NA

ULN: Upper limits of normal
NA: Not applicable
Mod G: Moderate grade of inflammation
Mod F: Moderate fibrosis

Supplemental Table 4

Type and Definition of Responses to Treatment for HBV Infection

Types	Alternative Terms	Definition
Virological Response		Undetectable HBV DNA by a sensitive PCR (20 IU/mL)
Primary Non-Response		< 1 log HBV DNA (IU/mL) decline from baseline at 3 months of treatment
Partial Response	Sub-Optimal Response	> 1 log decline, but detectable HBV DNA (IU/mL) after at 3 months of treatment
Secondary Non-Response	Virological Breakthrough	> 1 log increase from the nadir HBV DNA(IU/mL) level while on therapy in compliant patients
HBV Resistance	Anti-HBV Virological Resistance	Development of selected HBV variants with ammino acid substitution and reduced susceptibility to the same NA therapy
Virological Rebound	Relapse	Increase in serum HBV DNA to >20,000 IU/mL or above pre-treatment baseline level after achieving virological response, during continued therapy

Supplemental Table 5