الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

VIRAL HEPATITIS

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2018

		Anti-HBc		
Interpretation	**HBsAg**	**IgM**	**IgG**	**Anti-HBs**
Incubation period	+	+	-	-
Acute hepatitis				
Early	+	+	-	-
Established	+	+	+	-
Convalescence				
(3-6 months)	-	±	+	±
(6-9 months)	-	-	+	+
Post-infection				
> 1 year	-	-	+	+
Chronic				
Usual	+	-	+	-
Immunisation without infection	-	-	-	+

		Anti-HBc		
Interpretation	**HBsAg**	**IgM**	**IgG**	**Anti-HBs**
Incubation period	+	+	-	-
Acute hepatitis				
Early	+	+	-	-
Established	+	+	+	-

INTERPRETATION OF THE SEROLOGICAL DIAGNOSIS OF HBV infection

		Anti-HBc	
	HBsAg	IgM	IgG
Incubation period	+	+	-
Acute hepatitis			
Early	+	+	-
Established	+	+	+

Assessment of chronic HBV: *practical aspects*

Assessment of viral replication

HBeAg

HBV DNA

Assessment of liver disease

ALT, clinical features, bilirubin, albumin, PT,

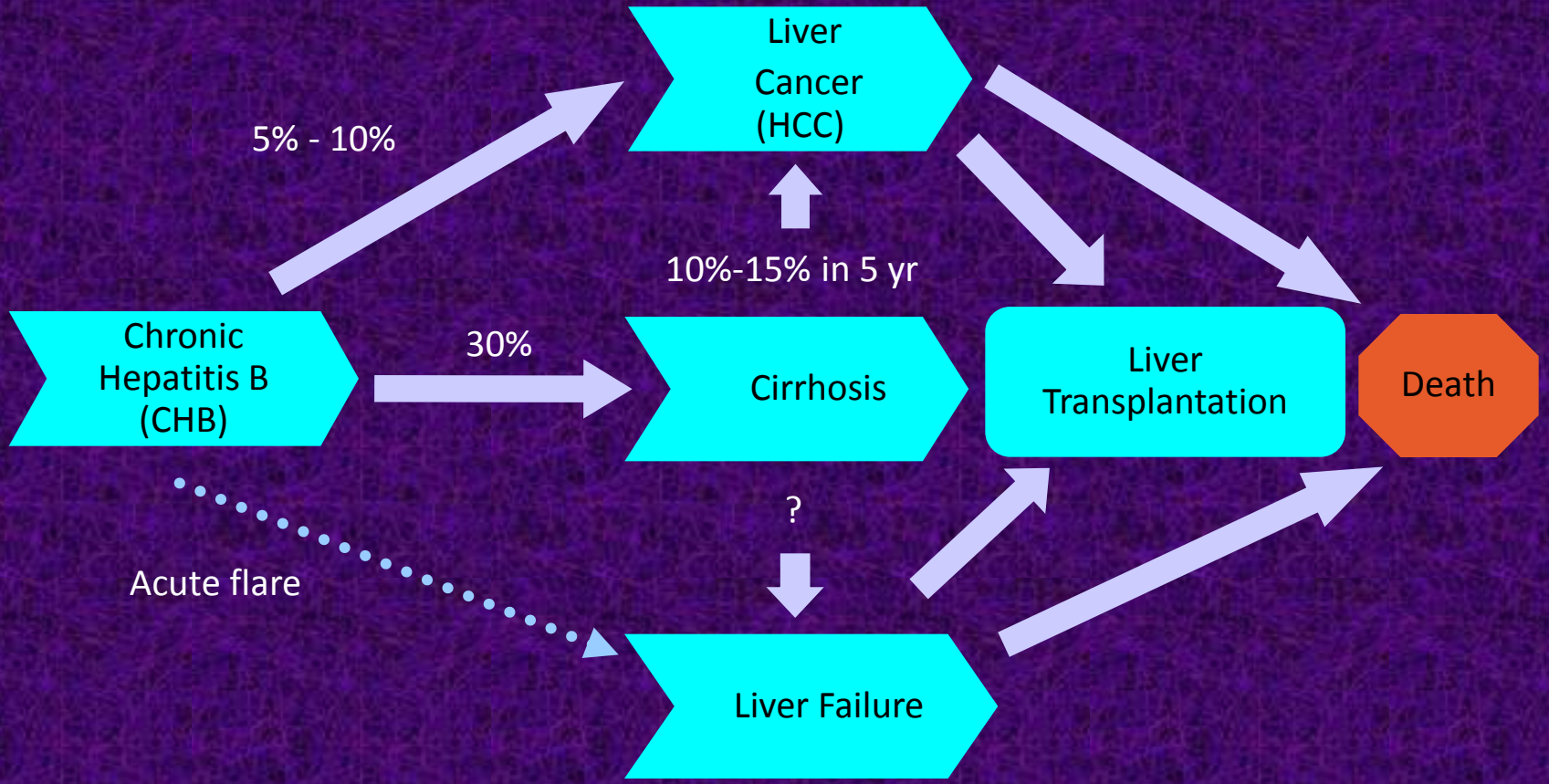
Hepatic imaging

Liver biopsy

In acute infection the hepatitis B surface antigen (HBsAg) is a reliable marker of HBV infection,

a negative test for HBsAg makes HBV infection very unlikely but not impossible

Disease progression occurs in 15–40% of chronic hepatitis B patients



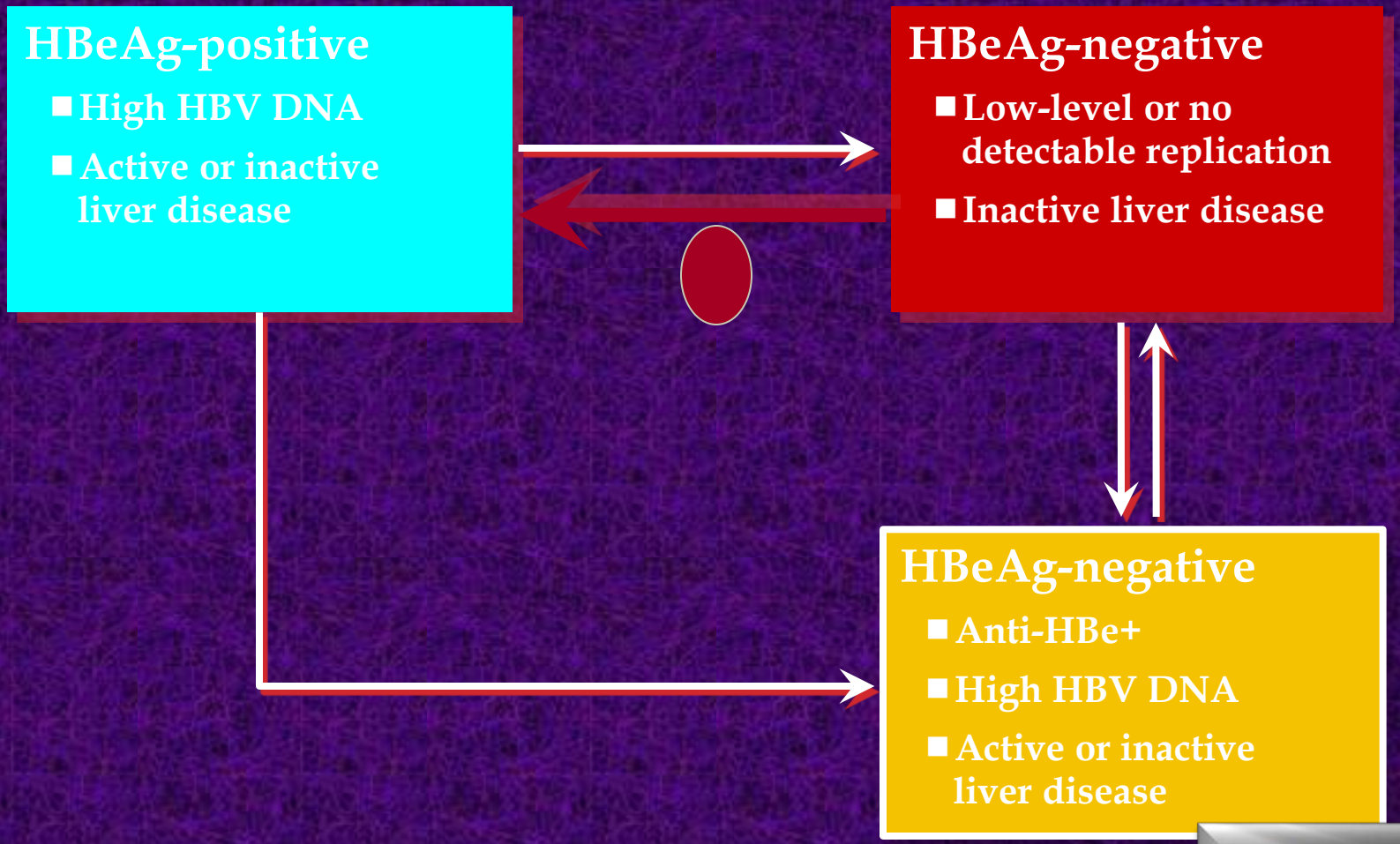
Fattovich G, et al. Gastroenterology 2004;127:S35-50

Torresi J, et al. Gastroenterology 2000;118:S83-S103.

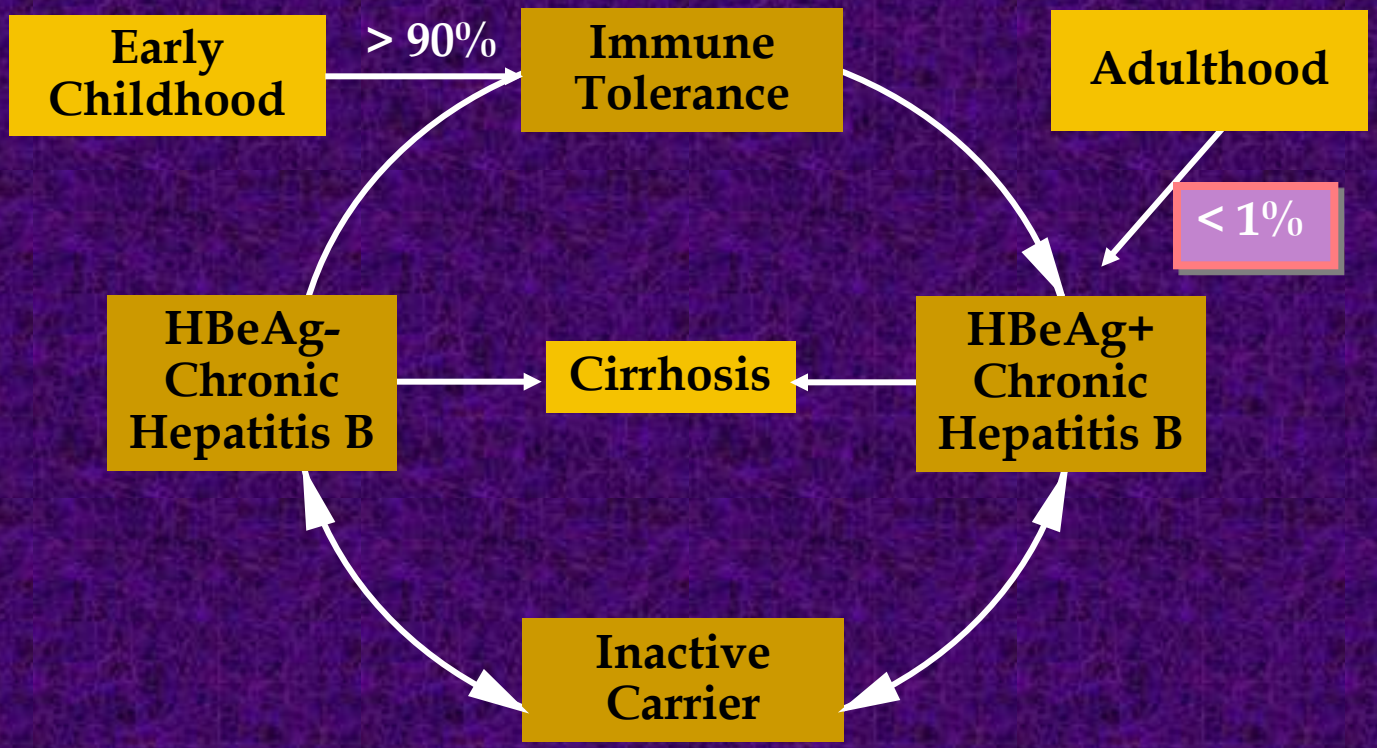
Fattovich G, et al. Hepatology 1995;21:77-82.

Perrillo R, et al. Hepatology 2001;33:424-432.

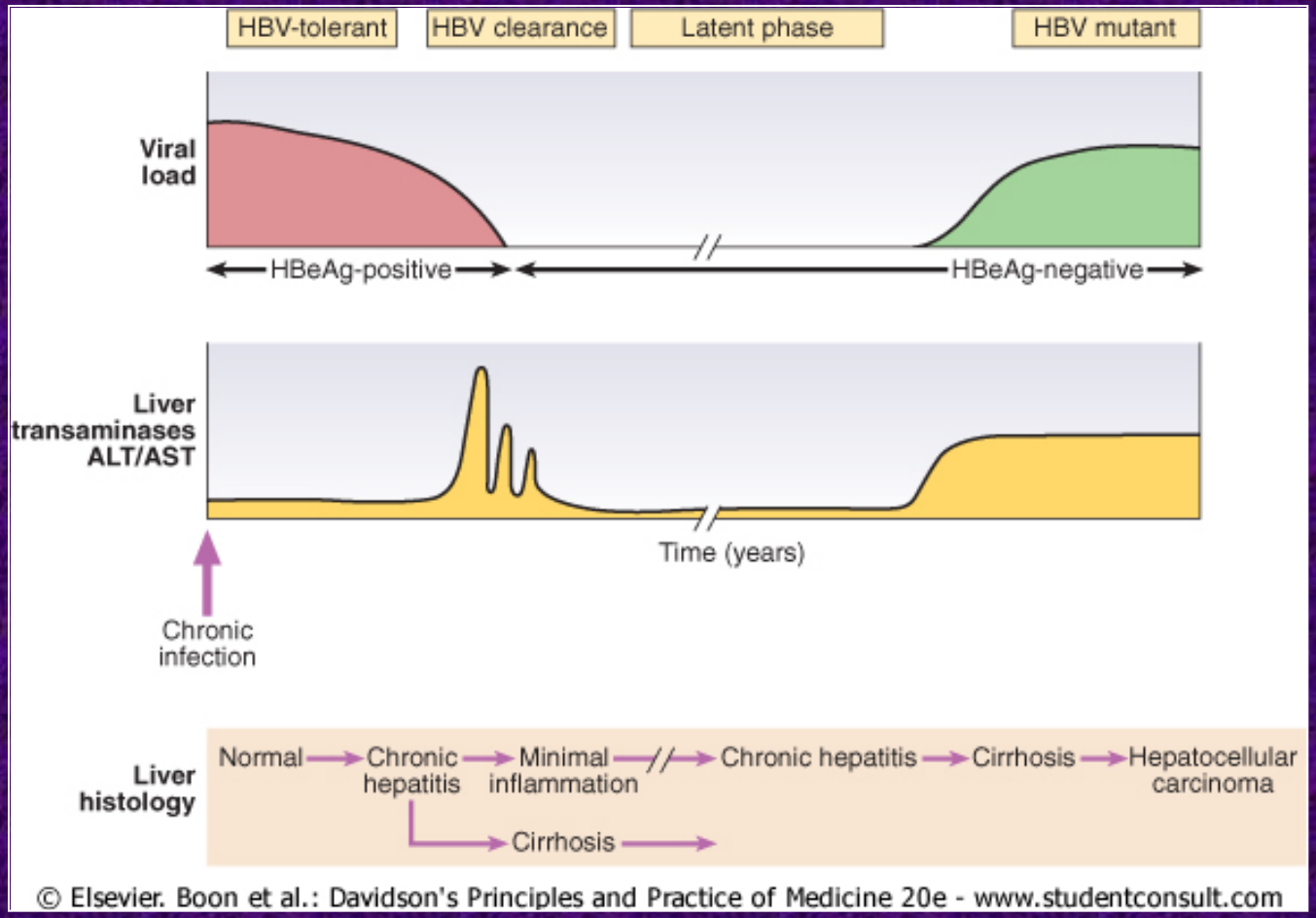
Categories Of Chronic HBV Infected Patients



Natural History of HBV Infection



Chen DS, et al. J Gastro Hep. 1993.
Seeff L, et al. N Engl J Med. 1987.



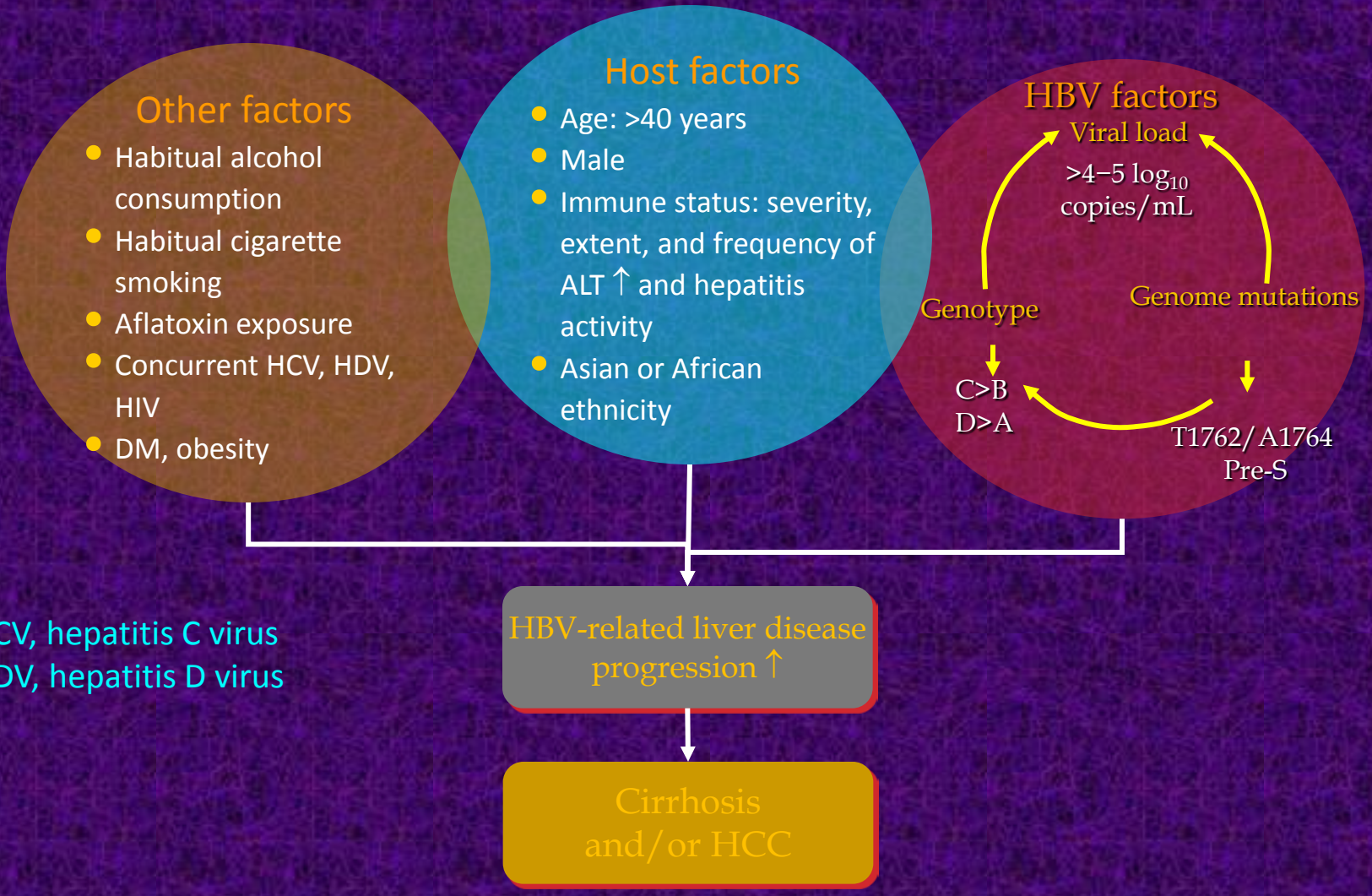
HBV disease burden

- Diverse and variable spectrum of natural history and chronic disease

ESLD: End-stage liver disease
HCC: Hepatocellular carcinoma

EASL CPG. J Hepatol 2009

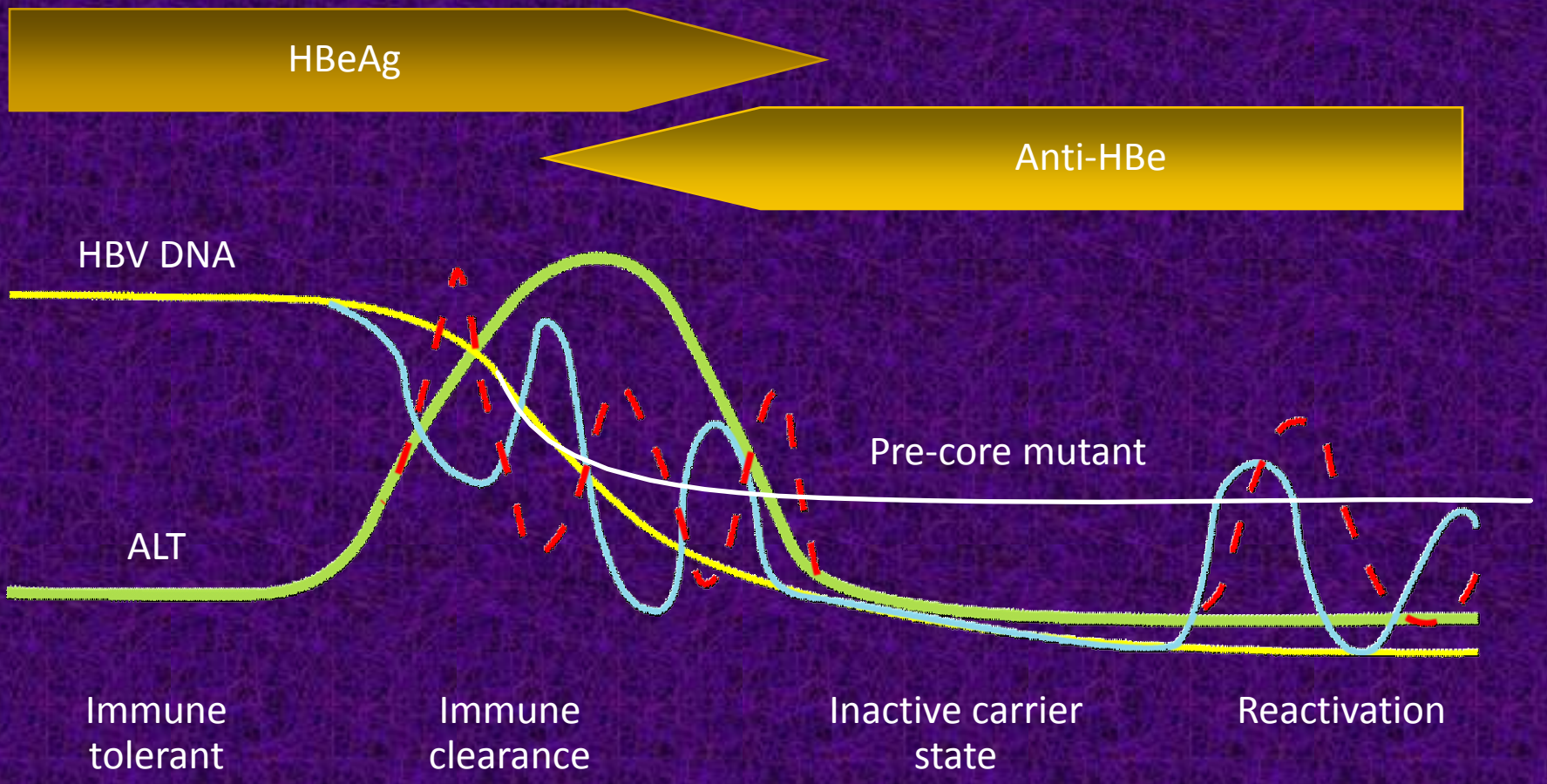
Factors affecting differences in the course of disease



HCV, hepatitis C virus
HDV, hepatitis D virus

Liaw YF *et al. Liver Int* 2005; 25: 472–89;
Fattovich G *et al. J Hepatol* 2008; 48: 335–52; Kao JH. *Hepatol Int* 2007; 1: 415–30.

Phases of chronic HBV infection



Adapted from Yim JY, Lok ASF. *Hepatology* 2006; 43: S173–81.

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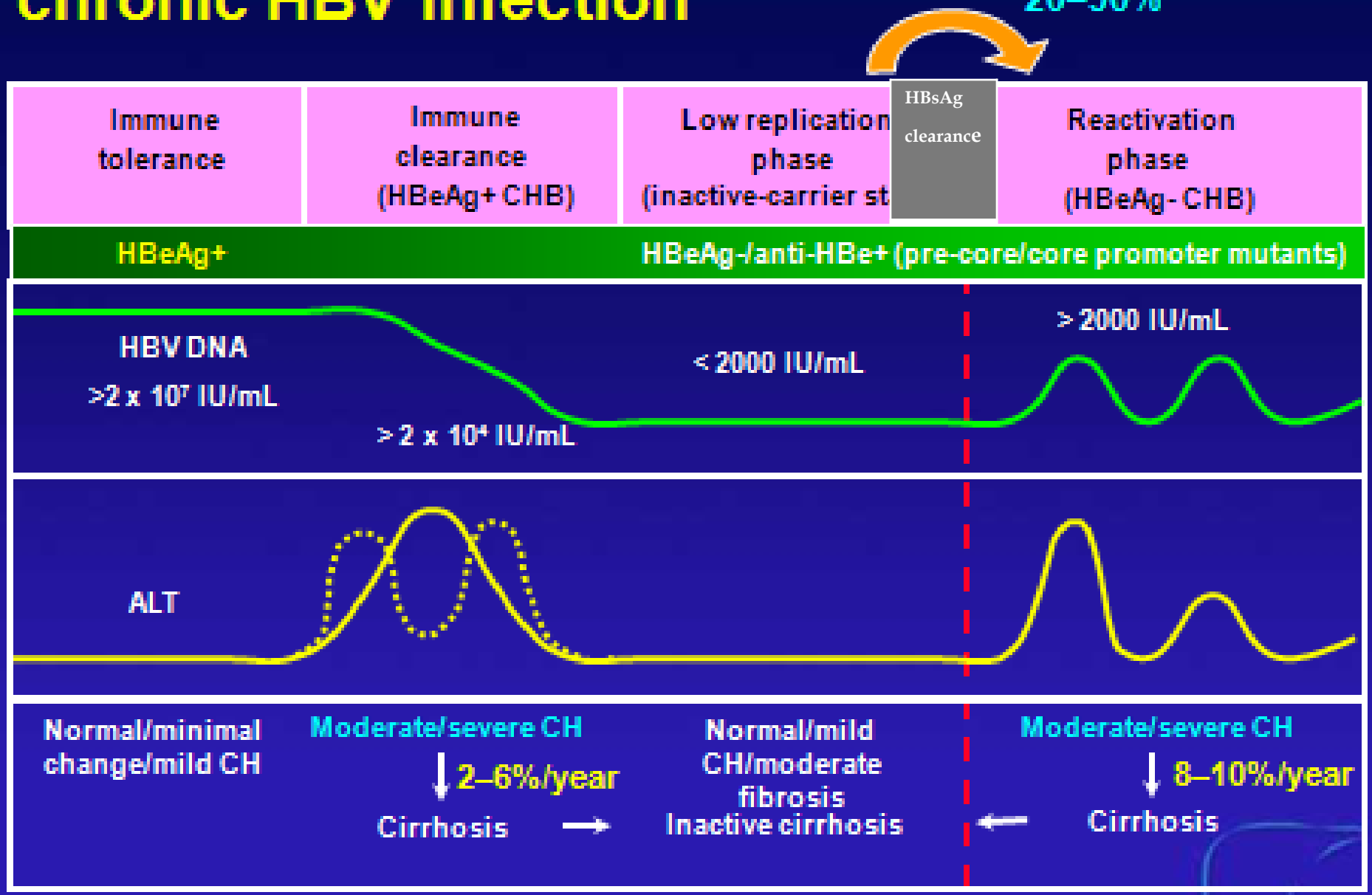
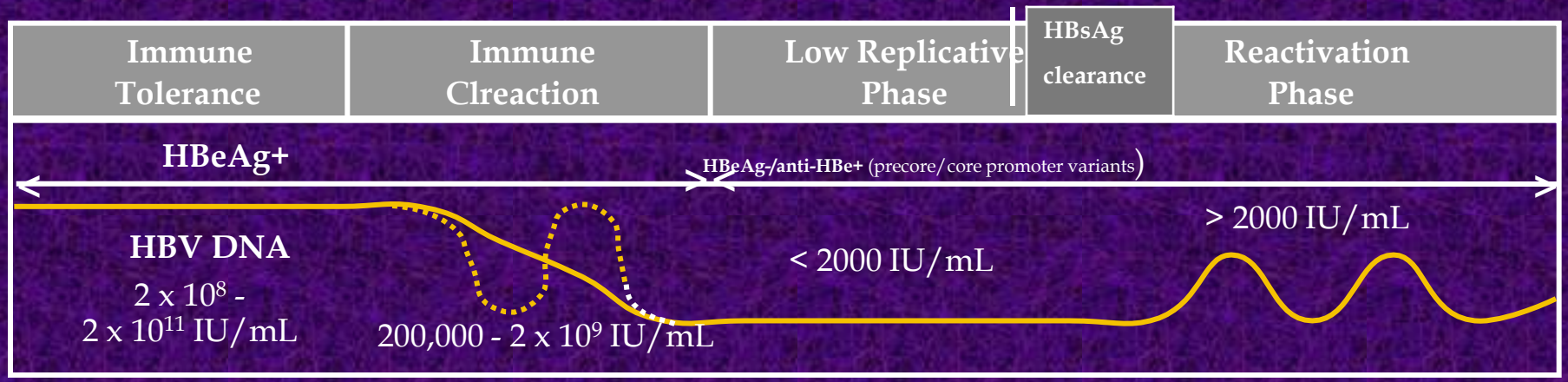
Chronic hepatitis B Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	$>10^7$ IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liv er disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

Natural history of perinatally acquired chronic HBV infection



Modified from Lok AS *et al. Hepatology* 2007; 45: 507–39; Pungpapong S *et al. Mayo Clin Proc* 2007; 82: 967–75.

Phases of Chronic HBV Infection

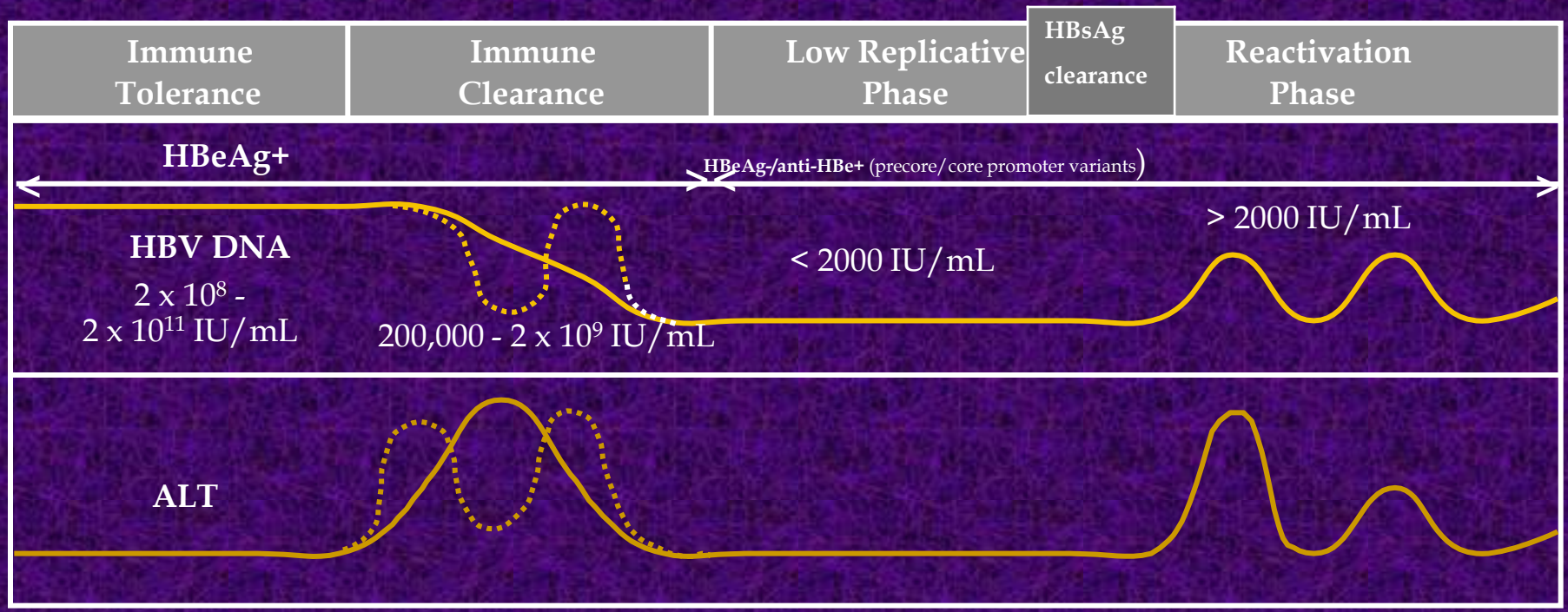


Immune tolerance phase

- In perinatally infected persons
  May persist 10 -30 years

Short lived or absent in childhood or adult-aquired HBV infection

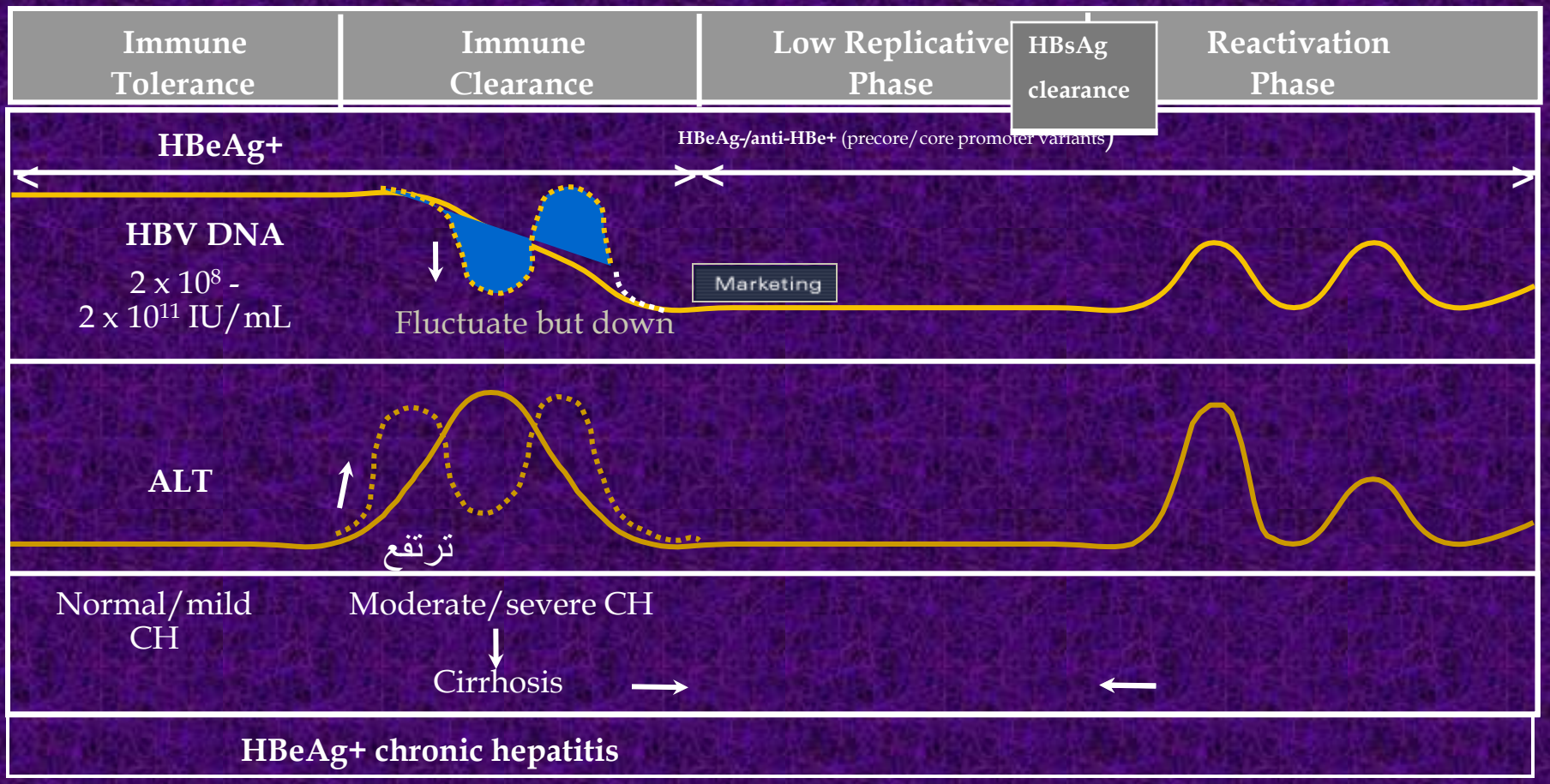
Phases of Chronic HBV Infection



Immune clearance

- Immune system mount an attack on infected hepatocytes

Phases of Chronic HBV Infection



Inactive carrier

- 15 -24 % develop HBeAg chronic disease
- 1-17 %sustained reversion back to HBeAg positivity

- Fattovich 2008
- Chu cm 2004

Immune tolerance phase

- In perinatally infected persons
  May persist 10 -30 years

Short lived or absent in childhood or adult-aquired HBV infection

Immune Reaction (clearance)

- Immune system mount an attack on infected hepatocytes

- HBV Tested markers for Diagnosis?

Screening for HBV

- HBsAg
- Anti-HBc

If positive

- HBV DNA PCR

- HBV Tested markers for Diagnosis?
- HBsAg
- HbeAg
- Anti-Hbe

- HBV DNA PCR

- HBV Tested markers for Diagnosis in immunosuppressed patients ?

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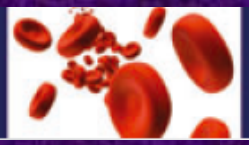
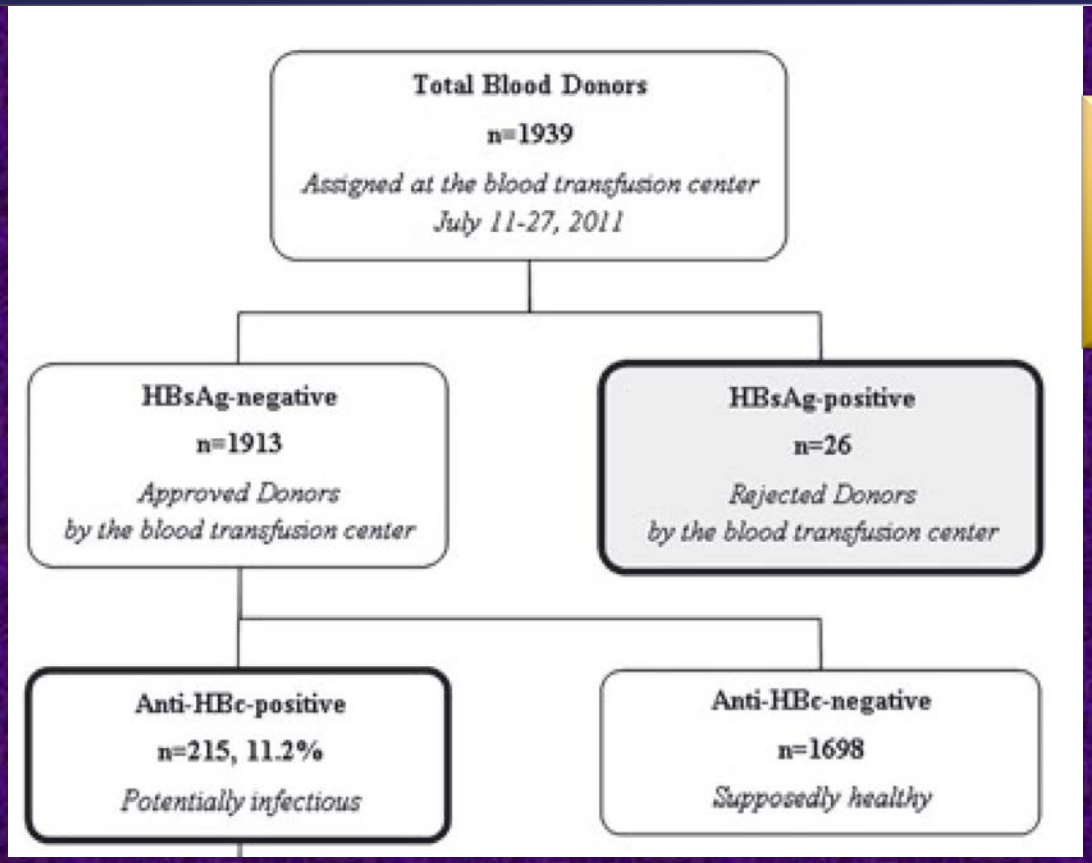
Significance of screening antibodies to hepatitis B virus core antigen among Syrian blood donors

TRANSFUSION MEDICINE
Official Journal of the British Blood Transfusion Society



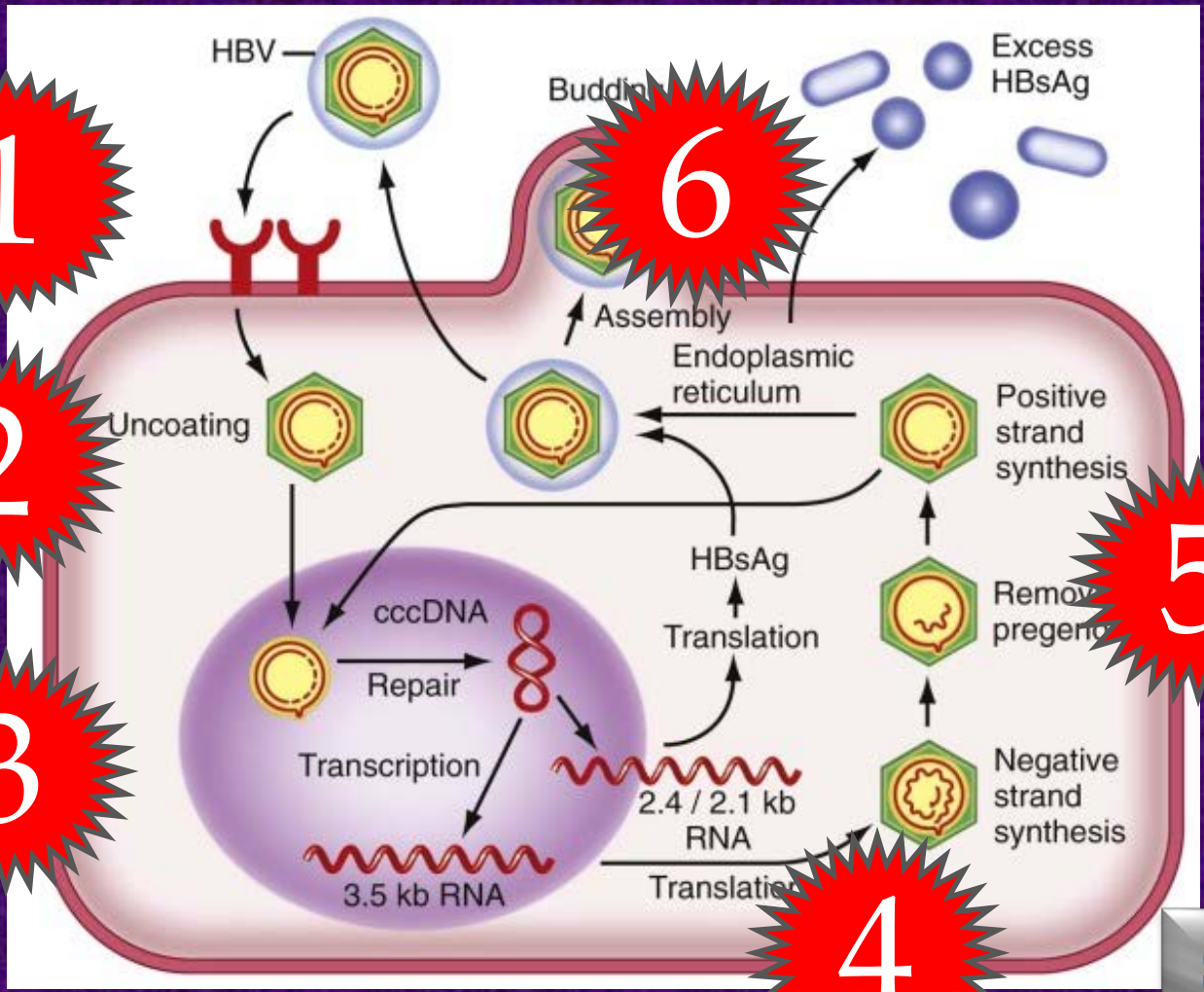


Healthy blood donors
1.3% HBsAg+

11.2% Anti-HBc+

W. Muselmani et al. Transfusion Medicine 2013

Life cycle of the hepatitis B virus (HBV)



Covalently Closed Circular DNA (cccDNA)

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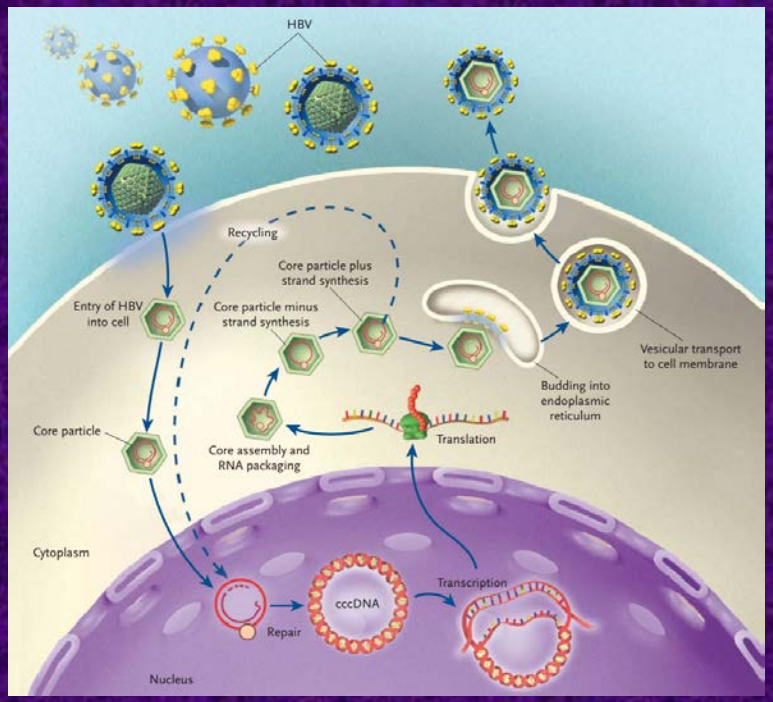
cccDNA



- Very stable within the hepatocyte
- Persist after antiviral therapy and even after clearance of HBsAg
- Plays a significant role in reactivation of disease

Werle-Lapostolle et al (2004) Gastroenterology 126:1750

N Engl J Med 2004;350:1118-29

Covalently Closed Circular DNA (cccDNA)

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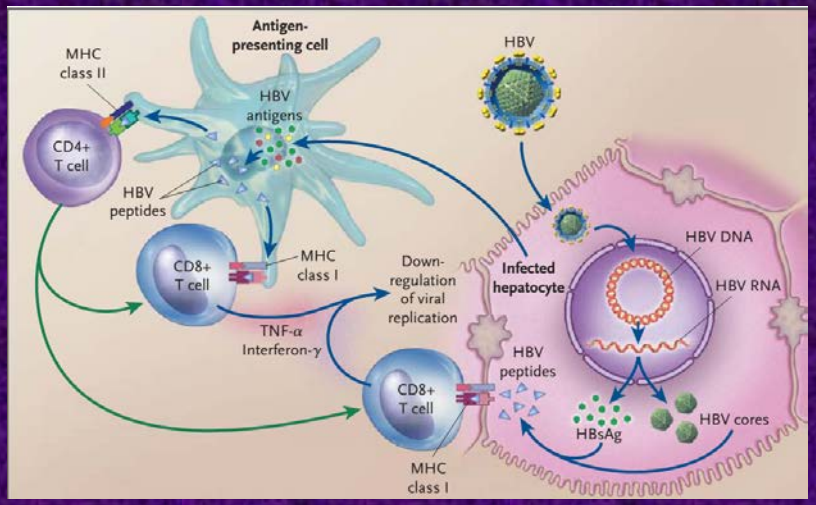
HBV Pathogenesis



- HBV is not directly cytopathic
- Greatest damage to the host is self-inflicted
  - immune response
- Enhanced immune clearance of HBV ⇨ increasing damage to the liver
  - fulminant hepatitis

Screening for HBV

- HBsAg
- Anti-HBc

If positive

- HBV DNA PCR

HBV Tested markers for Diagnosis?

- HBsAg
- HbeAg
- Anti-Hbe

- HBV DNA PCR

Antiviral Options

Antiviral Drug	Usual Daily Dose (If Normal Renal Function)	Risk of Resistance after 1-year treatment
Lamivudine	100 mg	20%
Adefovir	10 mg	5%
telbivudine	600 mg	20%
Entecavir	0.5 mg	0%
Tenofovir	300 mg	0%

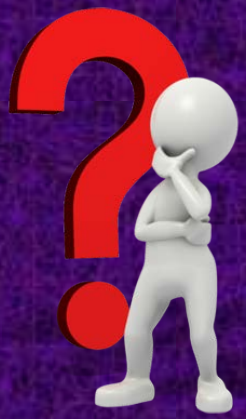
High barrier to resistance

Which patient group may need individualised management ?

Should some HBeAg-positive patients with chronic HBV infection be treated?

Should some patients have more frequent HCC monitoring?

In which patients should PEG-IFN therapy be considered?



If my patient has impaired renal function do I need to modify the NA dose?

Can NA treatment be stopped in some HBeAg-negative patients before HBsAg loss?

Do I have to change the monitoring schedule in patients with comorbidities?

What is the best management pathway for patients at risk of reactivation?

What is the optimal treatment for patients with renal or bone abnormalities?

Natural molecular variants of HBV

- **HBeAg positive (wild type)**[1]
  - Associated with higher serum HBV DNA levels and greater infectivity[2]

  Mixed infection/ ? Transitioning to HBeAg –ve disease

- **HBeAg negative (genetic mutations at pre-core or core promoter regions)**
  - Associated with poorer long-term clinical response to therapy and lack of spontaneous remission
  - Abolishes HBeAg production (HBeAg-negative CHB)

HEPATITIS B DNA (VIRAL LOAD) AND DISEASE PROGRESSION

HBV DNA is an independent risk factor for HCC and cirrhosis

Primary goal of hepatitis B therapy

Durable suppression of
active HBV replication

Impact of viral suppression on liver disease outcomes

HBsAg SEROCONVERSION: THE CHAMPION AMONG ENDPOINTS

Measurement of the viremia is now the main test

- for the initial evaluation of the patient
- for the indication of the treatment
- for the follow up of the patient under treatment

Liver biopsy is not anymore mandatory

Fibrosis and Cirrhosis

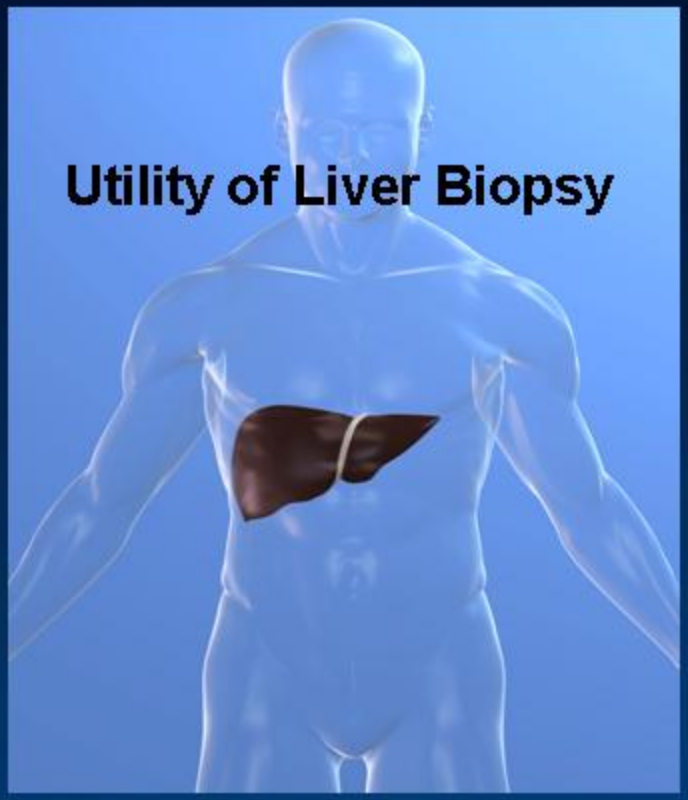
- Cirrhosis is a diffuse process characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodules

Cirrhosis may be considered irreversible

Normal liver | Mild fibrosis (scarring) | Moderate fibrosis | Cirrhosis

Feldman M, et al. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease. 6th Ed.* Philadelphia, PA. 199
Riley TR, Bhatti AM. *Am Fam Physician*. 2001;64:1736-1740.

Utility of Liver Biopsy



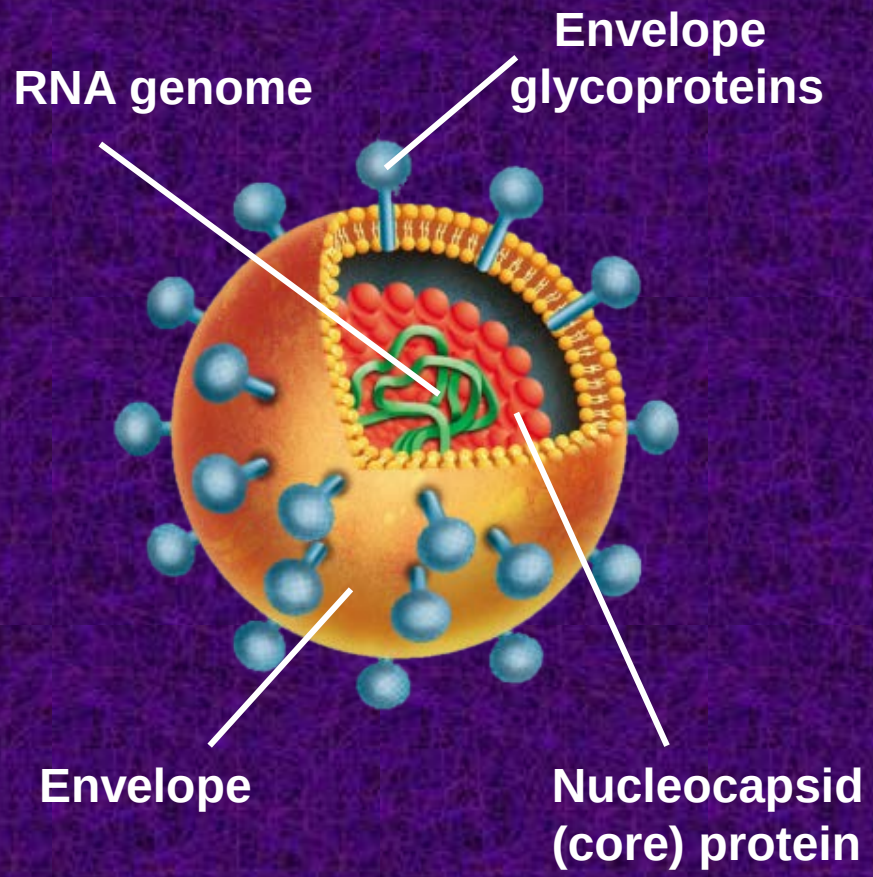
- Confirm presence of CHC
- Assess severity of necroinflammation
- Assess fibrosis
- Evaluate possible concomitant disease processes
- Assess therapeutic intervention

1. Brunt E. *Hepatology*. 2000;31:241-246.
2. Dienstag JL. *Hepatology*. 2002;36:S152-S160.
3. Herrine SK, Friedman LS. *J Hepatol*. 2005;43:374-376.

The hepatitis C virus

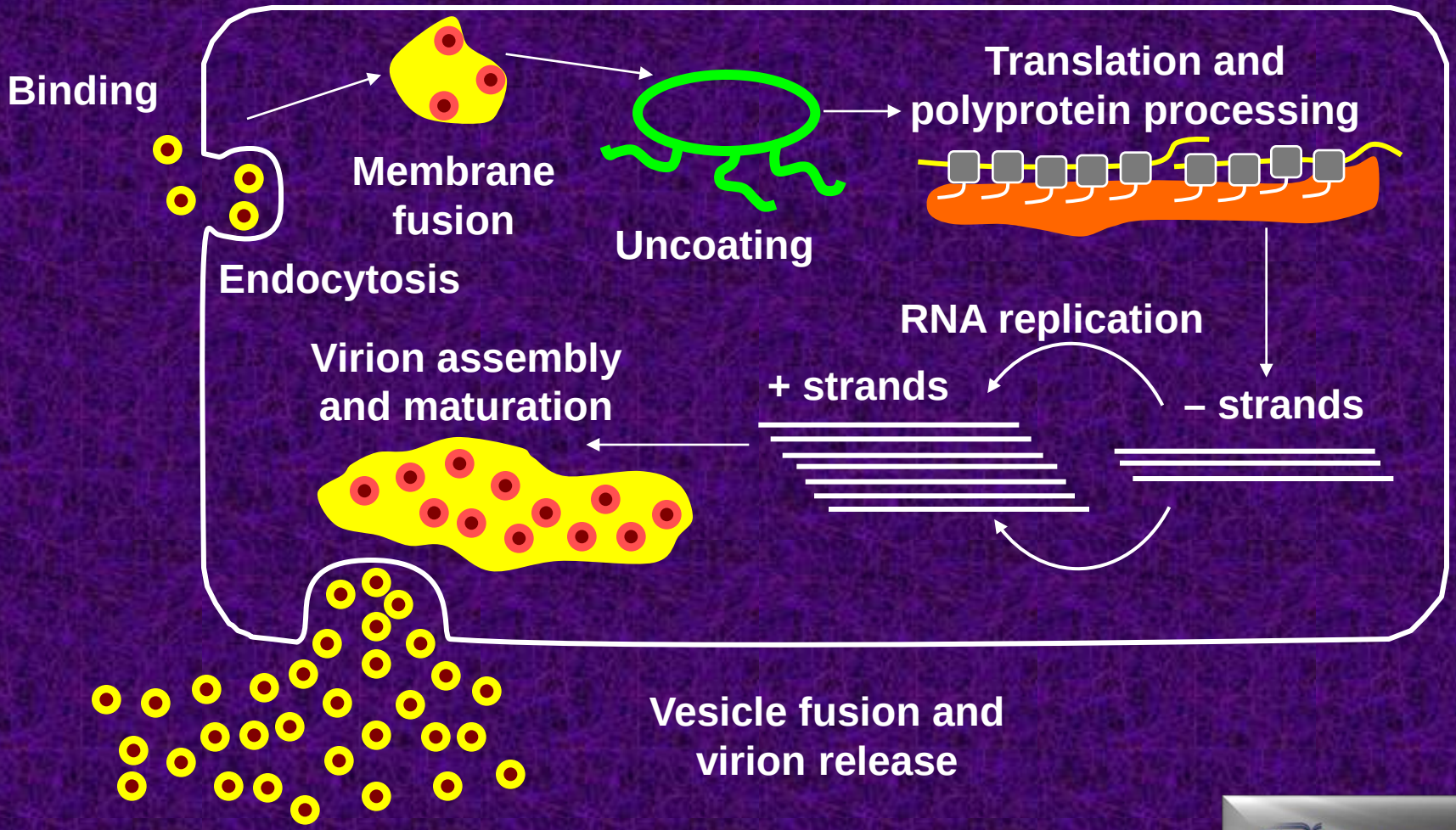
HCV characteristics

- Family Flaviviridae[1]
- Half-life: ≈2.7 hours[2]
- Daily production: 10 trillion (10^{12}) virions[2]
- Positive-sense single-stranded RNA (9.6 kb)[1,3]
- 3000-amino acid polyprotein[3]
- Enveloped[4]
- No RNA polymerase proofreading ability[4]



1. Purcell R. NIH Consensus Conference on Hepatitis C. 1997; 2. Neumann A, et al. Science 1998; 282: 103
3. Rosenberg S. J Mol Biol 2001; 313: 451; 4. Lauer G & Walker B. N Engl J Med 2001; 345: 41

HCV life cycle



Davis G et al. Semin Liver Dis. 1999; 19(suppl 1): 103