Clinical Case

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Clinical Case

- 70 year-old male
- Smoker, no alcohol intake
- No risk factors
- Diabetes Mellitus treated with oral antidiabetics
- June 2016 Asthenia and Anorexia
- **Physical examination:**
  - Normal
  - Abdomen soft and tender. No hepatomegaly neither splenomegaly

Lab Test

Hb 15 g/dL, **WBC** 5.600, **Plateles** 187.000,
Prothrombin time 99%, **INR** 1.01, **creatinine** 0.85 mg/dL
Total Bilirubin 1.9 mg/dL [0.29- 1.02], **eGFR** 72ml/min/1.73 m^2
AST 732 IU/mL [12- 40], **ALT** 1045 IU/mL [8- 44]
AP 110 IU/mL [35- 110], **GGT** 157 IU/mL [9- 55]
Abdominal US: Mild Liver Steatosis

AntiHCV -ve
HBsAg +ve
IgM HAV -ve
IgM HEV –ve
AntiHIV -ve

→

Ig M antiHBc +ve
HBeAg +ve
antiDelta -ve
HBV DNA >1x10E8 IU/mL

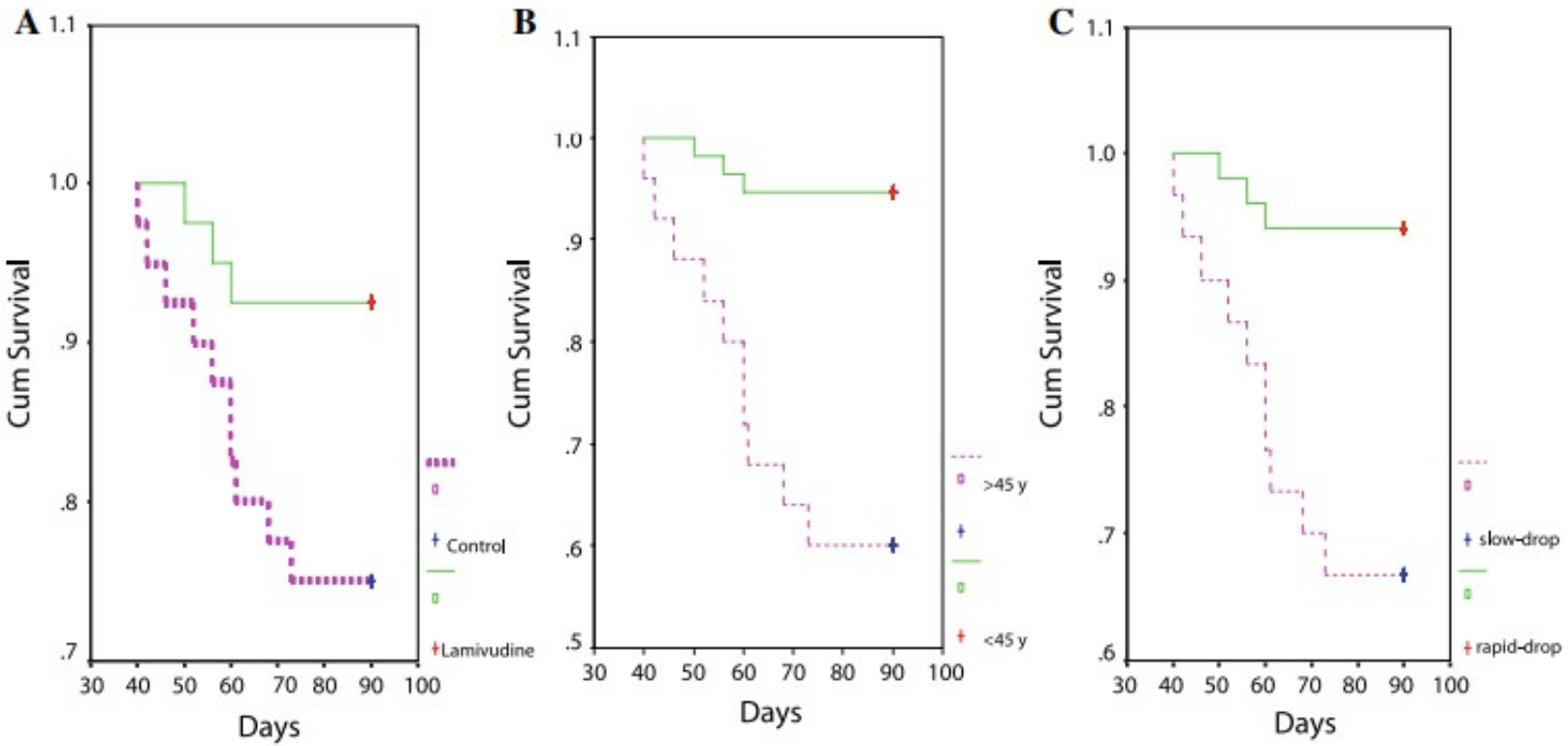
✓**Acute hepatitis B**

Do you consider HBV Therapy for this patient?

- Yes
  - Nucleoside Analogue
  - Interferon
- No

Effects of Treatment, Age and HBV DNA on survival in Severe Acute Hepatitis B

80 patients with severe acute hepatitis B randomly assigned to LAM or Placebo



Early treatment with lamivudine leads to mortality improvement in patients with severe acute hepatitis B

Yu JW et al. Dig Dis Sci (2010) 55:775–783

NUCs Therapy for Severe Acute Hepatitis B

- What is the appropriate definition
  - Recent onset of jaundice and coagulopathy (international normalized ratio (INR): 1.40–1.60) within a week
  - Prothrombin Index <40%

- Any Negative effect?
  - Lower rate of antiHBs seroconversion?

Special patient groups: acute hepatitis B

- Preventing the risk of acute or subacute liver failure is the main treatment goal
  - Treating to improve quality of life and reducing risk of chronicity are also relevant treatment goals

Recommendations	Grade of evidence	Grade of recommendation
More than 95% of adults with acute HBV hepatitis do not require specific treatment	II-2	1
Only patients with severe acute hepatitis B, characterized by coagulopathy or protracted course, should be treated with NAs and considered for liver transplantation	II-2	1

EASL CPG HBV. J Hepatol 2017;67:370–98

Clinical Case

December 2016 (6 months latter)

Hb 15 g/dL, **WBC** 5.600, **Plateles** 187.000,

TP 95%, **INR** 1, **creatinine** 0.85 mg/dL, Glucemia 110 mg/dl

Total Bilirubin 0.8 mg/dL

AST 140 IU/mL [12- 40], **ALT** 280 IU/mL [8- 44]

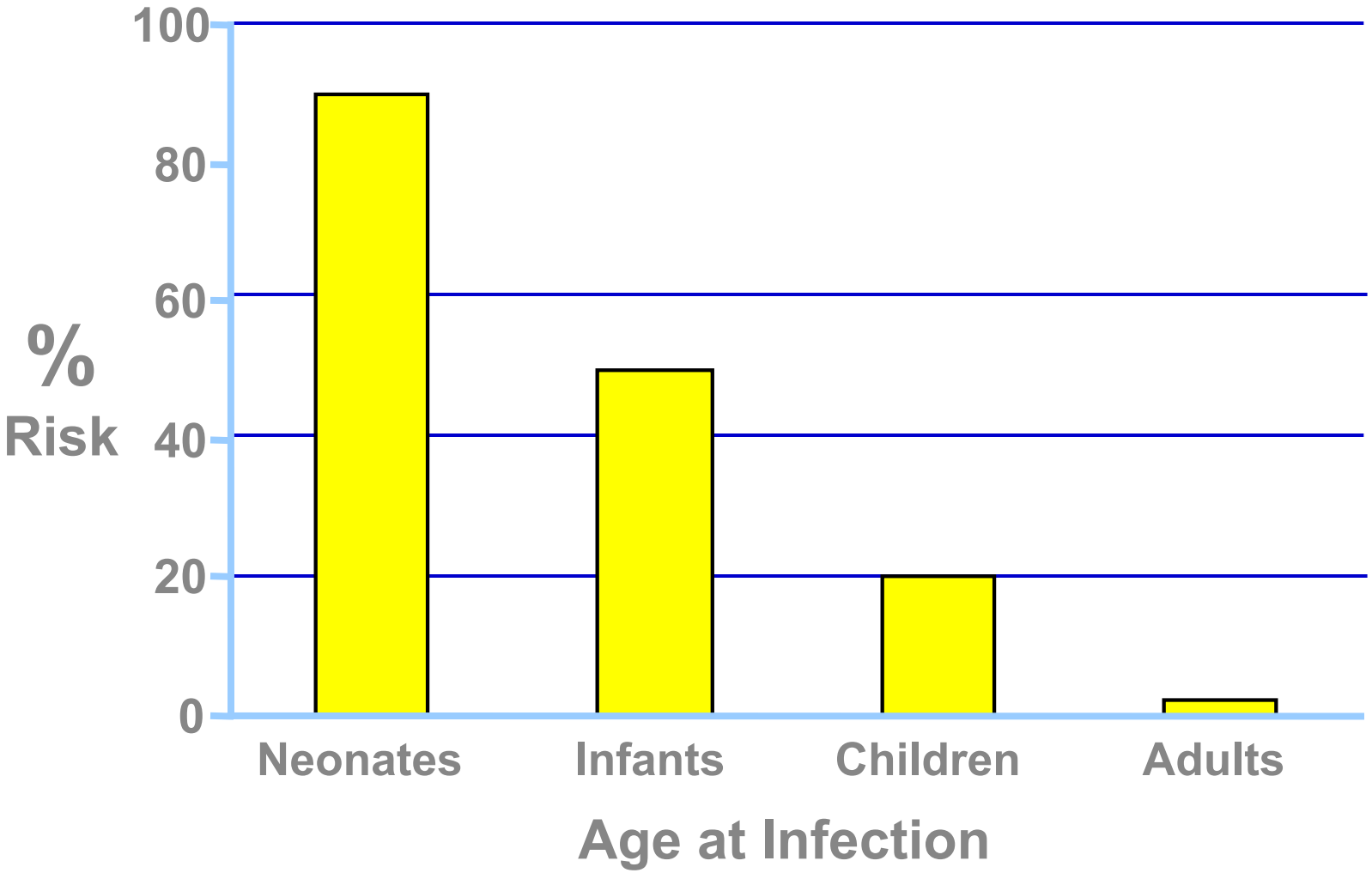
AP 110 IU/mL [35- 110], **GGT** 157 IU/mL [9- 55]

HBsAg positive, **antiHBc IgM** negative

HBeAg positive, **HBV-DNA** >1x10E8 IU/mL

HBV Genotype A

Risk of Chronic HBV Infection



Progression from acute to chronic hepatitis B is more common in older adults

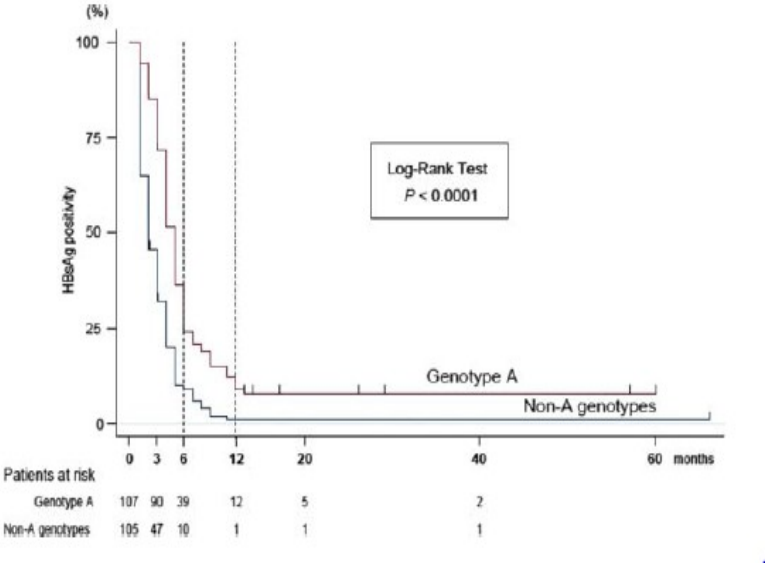
HBV clearance rates by gender, age, HIV status and clinical presentation

	Number	HBV cleared	HBV not cleared	Unknown	Clearance rate (%)	Chronicity rate (%)
Male	61	42	14	5	68.85	22.95
Female	15	15	0	0	100	0
Age <50	43	36	3	4	83.72	6.98
Age ≥50	33	21	11	1	63.64	33.33
HIV positive	6	4	2	0	66.67	33.33
HIV negative	58	44	10	4	75.86	17.24
Symptomatic	57	48	5	4	84.21	8.77
Asymptomatic	12	4	8	0	33.33	66.67

McKeating C et a. Ulster Med J 2018;**87:**177-180

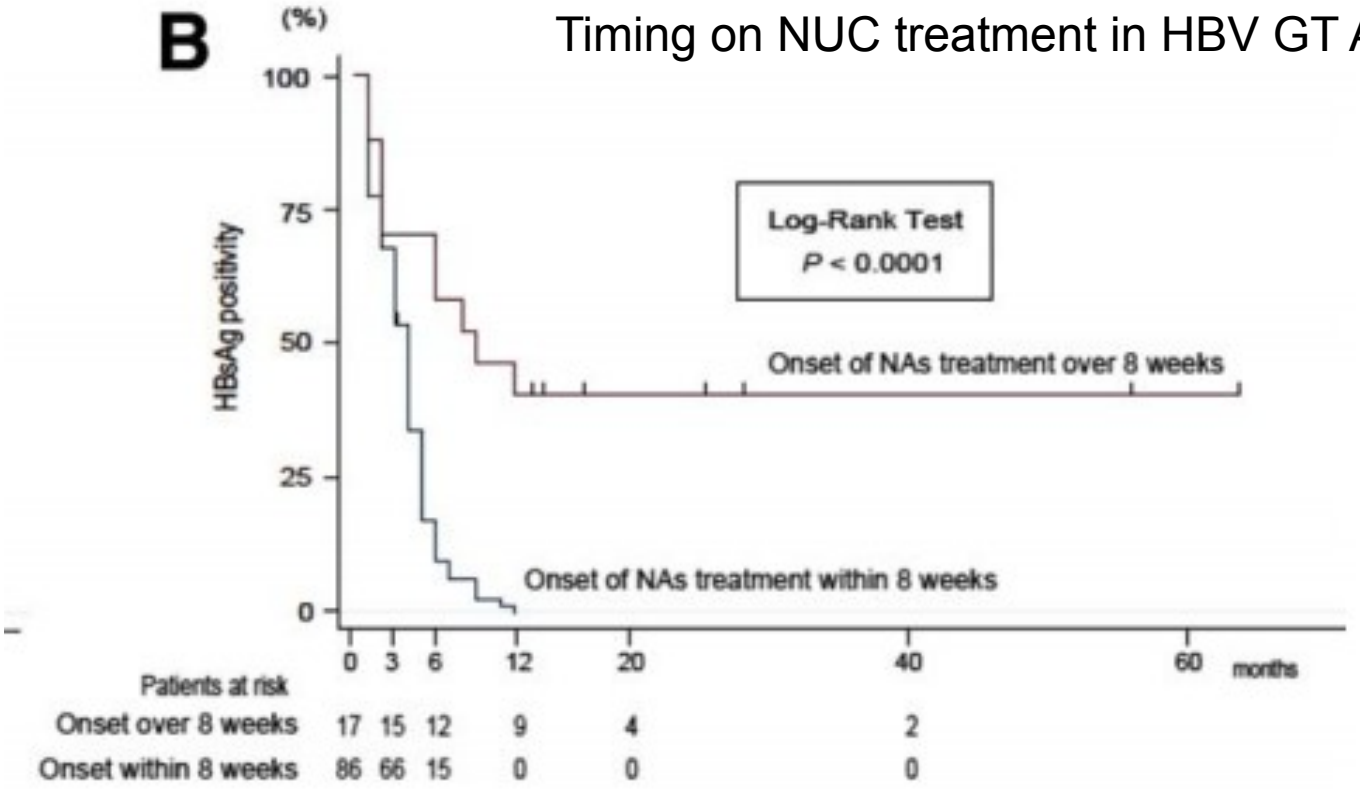
Risk Factors for Long-Term Persistence of HBsAg Following Acute HBV Infection in Japanese Adults

- 212 Acute Hepatitis B patients, anti-HIV-ve followed -up 6 mo
- HBsAg persisted longer for GT A patients
- Risk Factorsity
  - Genotype A,
  - Higher peak level of HBV DN
  - Lower peak of ALT



Ito k et al. Hepatology2014;59:89-97

Risk Factors for Long-Term Persistence of HBsAg Following Acute HBV Infection in Japanese Adults



Timing on NUC treatment in HBV GT A

Ito k et al. Hepatology2014;59:89-97

In which phase of the CHB ?

- Chronic Hepatitis B

- Chronic HBV Infection

Nomenclature for chronic phases

- The natural history of chronic HBV infection has been schematically divided into five phases

	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
Liver 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

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persisitently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
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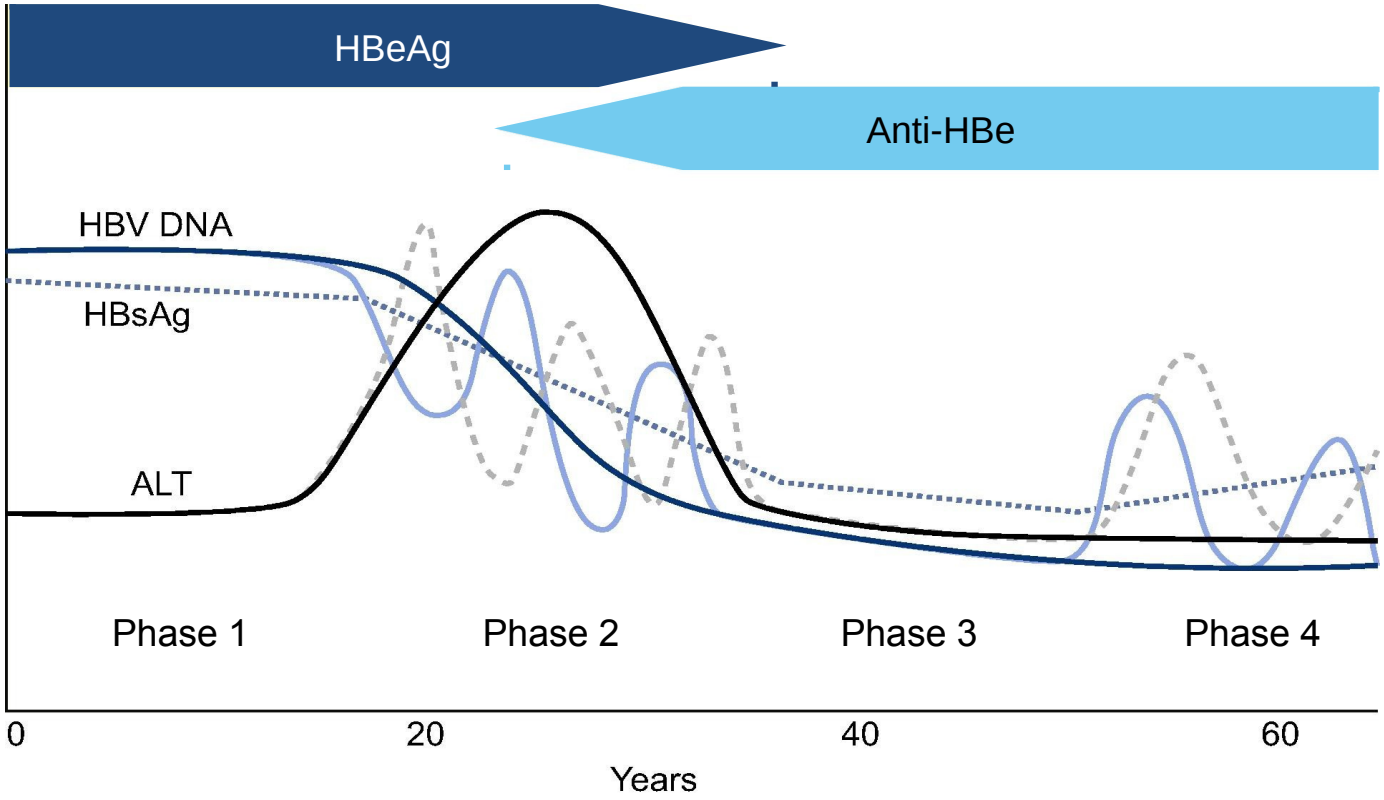
Phases of chronic HBV infection[1]



New nomenclature[2]	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B

1. Lok A, et al. J Hepatol 2017;67:847–61;
2. EASL CPG HBV. J Hepatol 2017;67:370–98

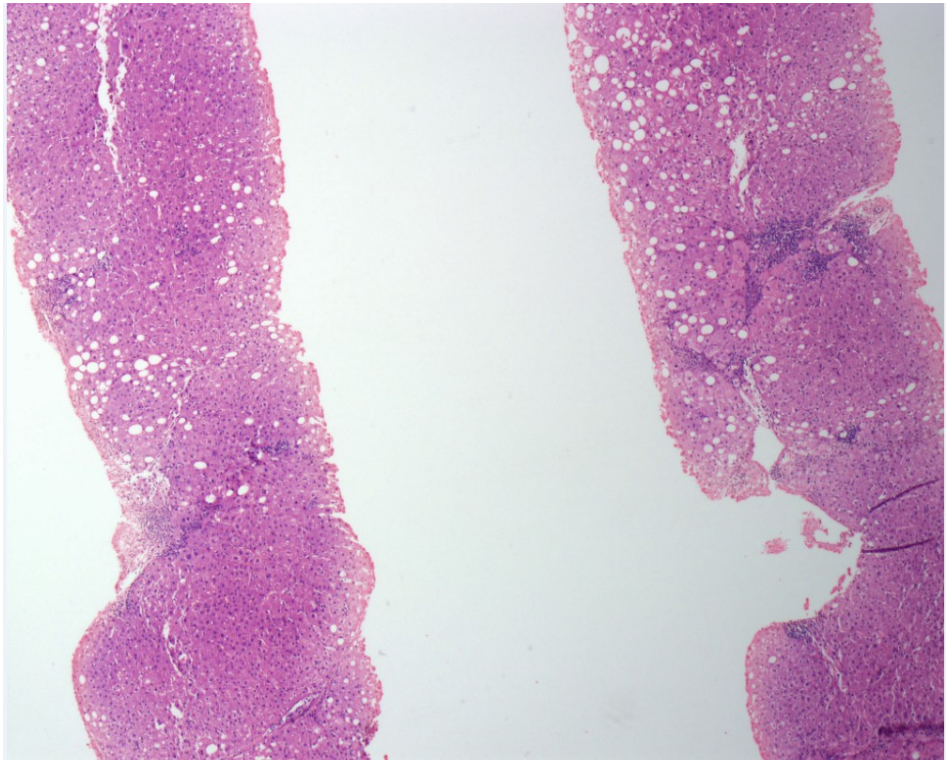
What do you recommend?

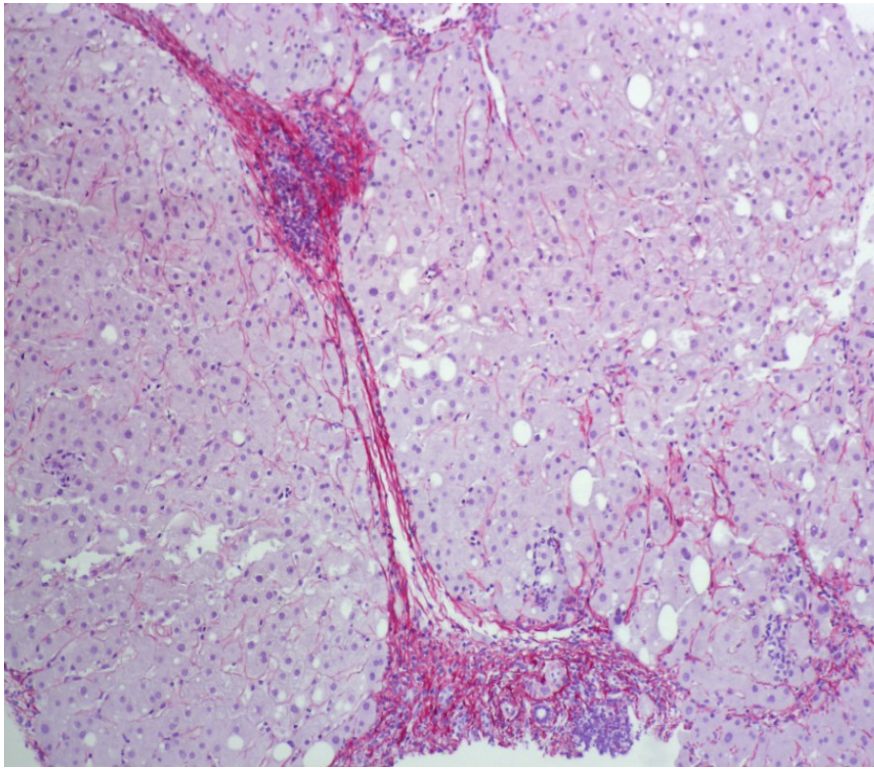
1.- Liver biopsy

2.- Transient Elastrography

3.- Start therapy without fibrosis assesment

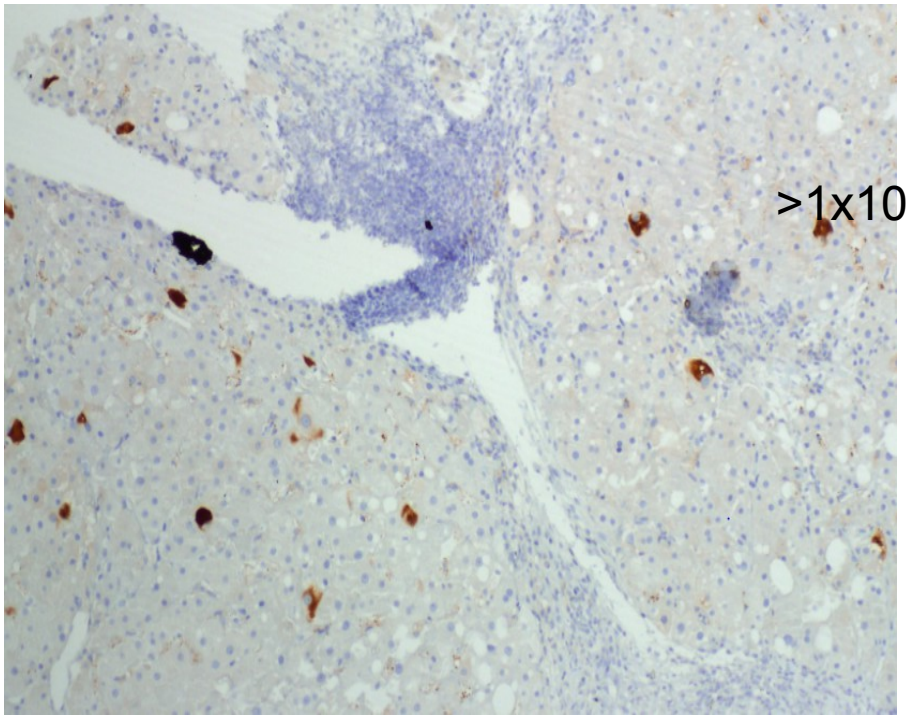
Liver Biopsy
Picrosirius Stain





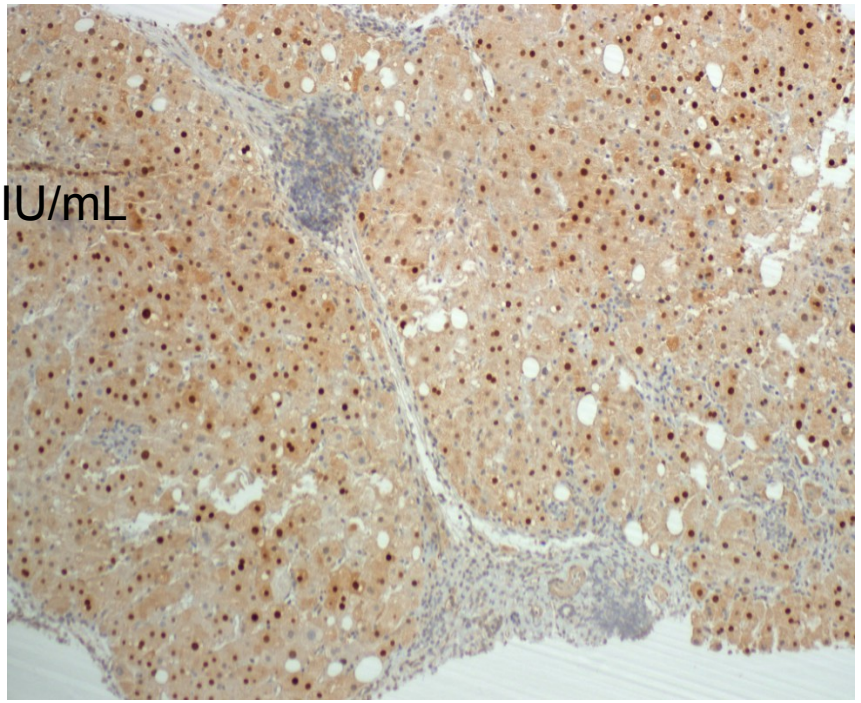
Specific Stains

HBsAg



>1x10E8 IU/mL

HBcAg



Liver biopsy showed histological changes of cirrhosis. Do you treat this patient?

- Yes, if he has elevated ALT
- Yes, if he has elevated ALT and HBV DNA
- Yes, indepedently of ALT levels
- No

Indications for treatment

- Primarily based on the combination of 3 criteria
  - HBV DNA, serum ALT and severity of liver disease

Recommendations	Grade of evidence	Grade of recommendation
Should be treated		
• Patients with HBeAg-positive or -negative chronic hepatitis B*	I	1
• Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level	I	1
• Patients with HBV DNA >20,000 IU/mL and ALT >2x ULN, regardless of severity of histological lesions	II-2	1
May be treated		
•Patients with HBeAg-positive chronic HBV infection† >30 years old, regardless of severity of liver histological lesions	III	2
Can be treated		
•Patients with HBeAg-positive or -negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations‡	III	2

*Defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis;
†Defined by persistently normal ALT and high HBV DNA levels;
‡ Even if typical treatment indications are not fulfilled
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Current treatment strategies for chronic hepatitis B: main concepts and features

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss*
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment AEs†	Probably not‡
Contraindications	Many§	None‖
Strategy	Induction of a long-term immune control	Inhibition of viral replication
Level of viral suppression	Moderate	Universally high
Effect on HBeAg loss	Moderate¶	Low in first year, moderate over long term
Effect on HBsAg levels	Variable¶	Low**
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance	No	Minimal to none††

*Stopping NAs after some years might be considered in selected cases; †Psychiatric, neurological, endocrinological; ‡Uncertainties regarding kidney function, bone diseases for some NAs; §Decompensated disease, comorbidities etc.; ‖Dose adjustments in patients with eGFR <50 ml/min are required for all NAs except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis); ¶Depending on baseline characteristics; **Slowly increases with treatment time in HBeAg-positive patients (a plateau in serological responses has been observed beyond treatment Year 4), usually very low in HBeAg-negative patients; ††So far no TDF or TAF resistance development has been detected

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Indications for selecting ETV or TAF over TDF*

- In some circumstances ETV or TAF may be a more appropriate treatment choice than TDF

Age	• >60 years
Bone disease	• Chronic steroid use or use of other medications that worsen bone density • History of fragility fracture • Osteoporosis
Renal alteration†	• eGFR <60 ml/min/1.73 m^2 • Albuminuria >30 mg/24 h or moderate dipstick proteinuria • Low phosphate (<2.5 mg/dl) • Haemodialysis

*TAF should be preferred to ETV in patients with previous exposure to NAs; †ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged ≥12 years and ≥35 kg body weight) with estimated CrCl ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis

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Follow-up

- Treatment with Entecavir 0.5 mg/day
- Patient remained asymptomatic
- 3 mo. ALT 80 IU/L, HBV DNA 20.000 UI/mL
- 6 mo. ALT 60 IU/L, HBV DNA 1.900 IU/mL
- US mild steatosis
- 1 year ALT 40, HBV DNA 160 IU/mL
  - HBsAg 2639, HBeAg positive
  - US Mild steatosis

Take home messages

- ✓ HBV is a common cause of acute hepatitis
- ✓ Progression from acute to chronic hepatitis B is more commonin older adults
- ✓ Therapy of acute hepatitis B should be individualized
- ✓ ETV, TDF and TAF are the recommended drugs for CHB therapy