CMEO
BriefCase

Critical Steps for Long-Term Management of HBV: Focus on Monitoring and HBV Reactivation

Supported by an educational grant from Gilead Sciences, Inc

CME OUTFITTERS

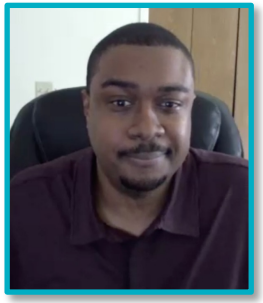
Joseph K. Lim, MD

Professor of Medicine
Director, Clinical Hepatology
Section of Digestive Diseases/Yale Liver Center
Yale University School of Medicine
New Haven, CT

Learning Objective

Routinely monitor patients with HBV every 6 months for disease progression, HCC, and HBV reactivation in patients who are immunosuppressed.

Patient Case: Thomas



- 31-year-old man who immigrated from Nigeria as a child
- Thomas has been diagnosed with CD20-positive B-cell non-Hodgkin's lymphoma
- His oncologist plans to initiate rituximab treatment

Audience Response

What would be your next step in alignment with ASCO recommendations?

A. Order routine blood tests
B. Schedule patient for treatment at the infusion center
C. Screen patient for Hepatitis B
D. Initiate antiviral treatment for Hepatitis B
E. I don’t know

Audience Response Rationale

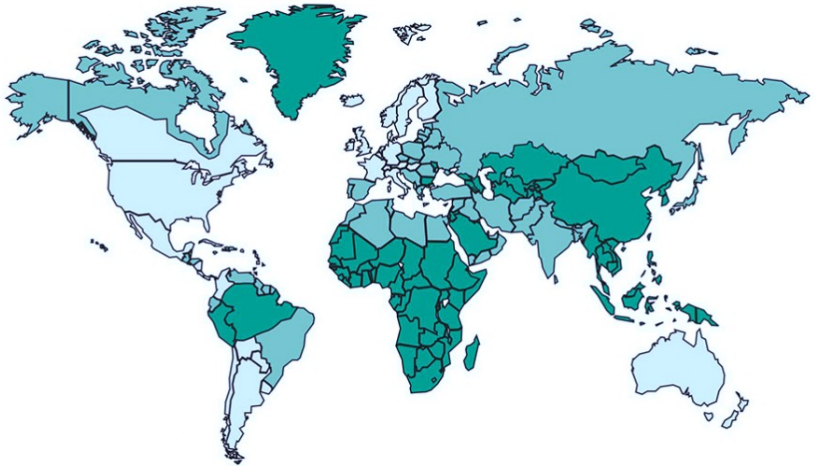
What would be your next step in alignment with ASCO recommendations?

A. Order routine blood tests
B. Schedule patient for treatment at the infusion center
C. Screen patient for Hepatitis B
D. Initiate antiviral treatment for Hepatitis B
E. I don’t know

Geographic Distribution of Chronic HBV Infection

Worldwide, 2006[1]

Region	HBV Prevalence ≥ 2%[2]
Africa	All countries
Asia	All countries
Caribbean	Antigua, Barbuda, Dominica, Grenada, Haiti, Jamaica, St. Kitts, St. Lucia, Turks & Caicos Islands
Central America	Guatemala, Honduras
Eastern Europe	All countries except Hungary
Middle East	All countries except Cyprus, Israel
North America	Indigenous populations in northern Canada
South America	Bolivia, Brazil, Colombia, Ecuador, Guyana, Suriname, Venezuela
South Pacific	All countries except nonindigenous populations of Australia and New Zealand
Western Europe	Malta, indigenous populations of Greenland



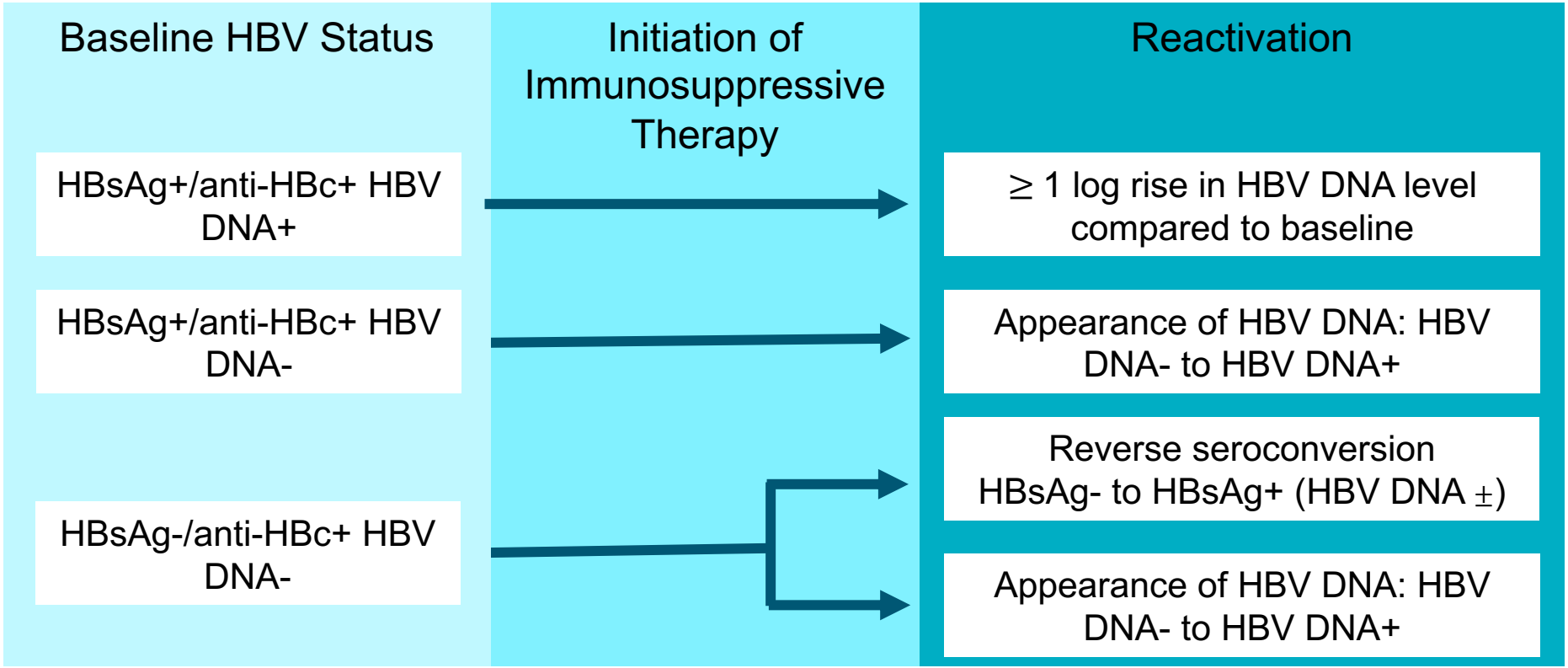
1. Travellers' Health; Yellow Book. http://wwwn.cdc.gov/travel/yellowbookch4-HepB.aspx. Accessed May 28, 2021.; 2. Abara WE, et al. *Ann Intern Med*. 2017;167:794-804.

HBV Reactivation: An Underappreciated, but Important Complication of Therapies

- New targeted treatment and biologics have revolutionized immunosuppression for patients with cancer, autoimmune diseases (rheumatoid arthritis, inflammatory bowel disease, psoriasis), and anti-rejection agents, but are associated with HBV reactivation (HBVr) at various levels of risk
- Additionally, HBVr occurs in patients with HBV-HCV coinfection receiving anti-viral agents
- Discontinuation of immunosuppression can have profound negative effects on disease control
- Premature cessation of chemotherapy may impact overall survival

Huang SC, et al. *Expert Rev Gastroenterol Hepatol*. 2020;14(7)565-578.

What is HBV Reactivation?



Hwang JP, et al. *J Clin Oncol*. 2015;33(19):2212-2220.

Are Patients Consistently Screened for HBV Prior to Chemotherapy?

11,959 adult patients receiving parental chemotherapy between 2012-2015

17.1% Were screened for either HBsAg or anti-HBc before chemotherapy (n = 2,045)

15.5% Had both HBsAg and anti-HBc before chemotherapy (n = 1,850)

HBV screening less likely to occur in community oncology clinics compared to teaching hospitals

Kwak YE, Stein S, Lim JK. *Dig Dis Sci.* 2018;63(1):61-71.

Immunotherapy and HBVr

- Immunotherapy with immune checkpoint inhibitors (ICIs) use has grown rapidly across a broad variety of advanced or metastatic malignancies
- Immunotherapy may lead to HBVr or immune-mediated hepatitis
- Hepatitis during immunotherapy may occur in patients with either current or past HBV infection

Wong G, et al. *Am J Gastroenterol*. 2021;116:1274-1283.

Scene 2: Virtual Visit

Audience Response

What serology test(s) should Dr. Franklin order for Thomas to confirm HBV status?

A. HBsAg prior to, or at the beginning of rituximab therapy
B. anti-HBc total IgG prior to, or at the beginning of rituximab therapy
C. HBsAg, anti-HBc total IgG, and anti-HBs prior to, or at the beginning of rituximab therapy
D. HBV DNA prior to the beginning of therapy
E. I don’t know

Audience Response Rationale

What serology test(s) should Dr. Franklin order for Thomas to confirm HBV status?

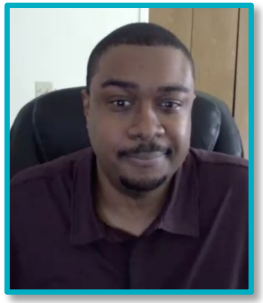
A. HBsAg prior to, or at the beginning of rituximab therapy
B. anti-HBc total IgG prior to, or at the beginning of rituximab therapy
C. HBsAg, anti-HBc total IgG, and anti-HBs prior to, or at the beginning of rituximab therapy
D. HBV DNA prior to the beginning of therapy
E. I don’t know

Screening Tests for HBV in the Context of Immunosuppressive Drug Therapy

Society	Recommended Screening Tests
American Association for the Study of Liver Diseases (AASLD)[1]	HBsAg and anti-HBc total IgG
American Gastroenterological Association (AGA)[2]	HBsAg and anti-HBc
American Society of Clinical Oncology (ASCO)[3]	HBsAg and anti-HBc
Centers for Disease Control and Prevention (CDC)[4]	HBsAg, anti-HBc, and anti-HBs
European Association for the Study of the Liver (EASL)[5]	HBsAg, anti-HBc, and anti-HBs

1. Terrault N, et al. *Hepatology*. 2018;67(4):1560-1599.; 2. Reddy KR, et al. *Gastroenterology* ; 2015;148:215-219. 3. Hwang JP, et al. *J Clin Oncol*. 2020;38:3698-3715.; 4. Centers for Disease Control and Prevention (CDC) Available at https://www.cdc.gov/hepatitis/hbv/pdfs/ChronicHepBTestingFlwUp.pdf. Accessed June 15, 2021.; 5. EASL 2017 Practice Guidelines. *J Hepatol*. 67:370-398.

Patient Case: Thomas



- Thomas' serologic results return:
  - HBsAg, HBcAb positive
  - HBV DNA 850 IU/mL, ALT 29 U/L
  - Diagnosis of chronic HBV infection
- Further testing:
  - HCV Ab, HDV Ab, HIV Ab negative
  - Fibroscan elastography: 7.5kPa (stage 2 fibrosis)
  - Ultrasound: normal liver echotexture, no cirrhosis or focal liver mass

Scene 3: Virtual Visit

Audience Response

Based on the serologic results, what would be your next step?

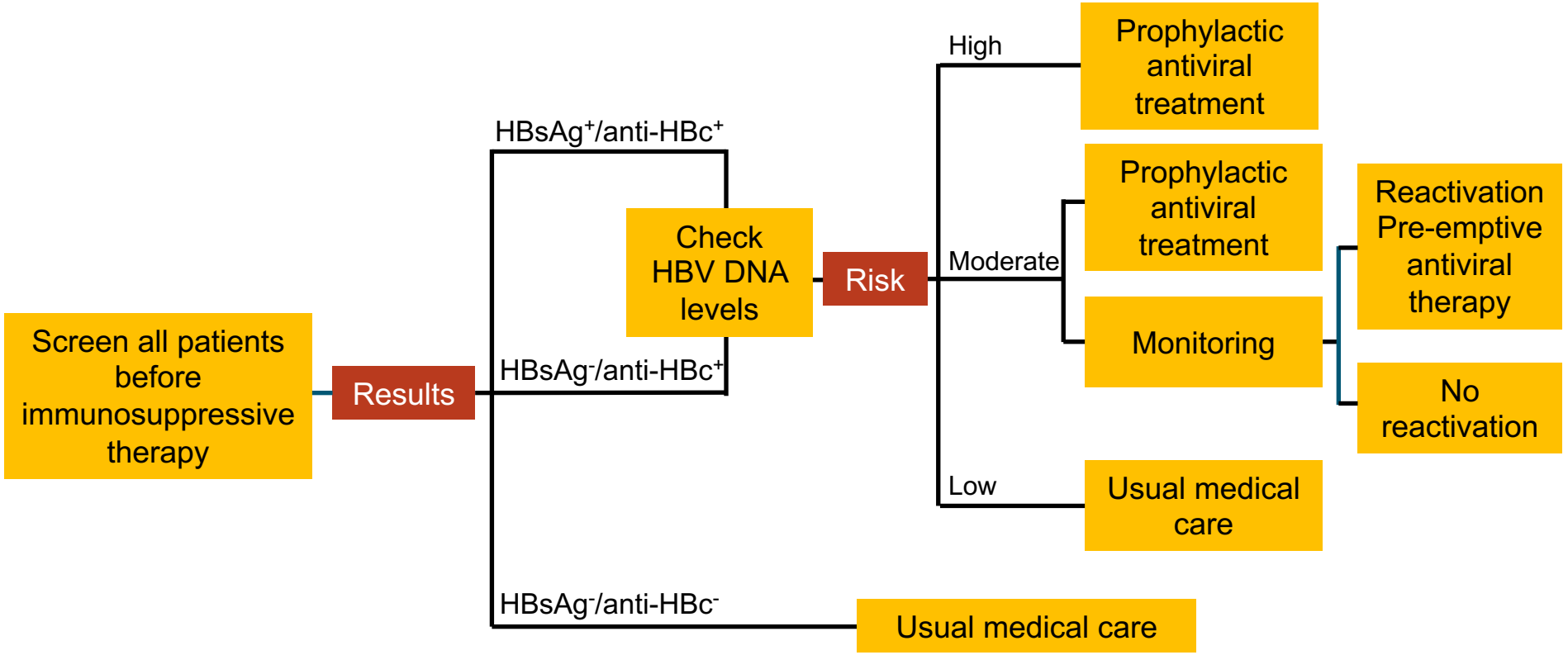
A. Delay rituximab treatment until you have a consult with hepatology
B. Continue with rituximab treatment and monitor his labs
C. Initiate prophylaxis with antiviral treatment for HBV
D. Cancel rituximab treatment due to risk of liver complications
E. I don't know

Audience Response Rationale

Based on the serologic results, what would be your next step?

A. Delay rituximab treatment until you have a consult with hepatology
B. Continue with rituximab treatment and monitor his labs
C. Initiate prophylaxis with antiviral treatment for HBV
D. Cancel rituximab treatment due to risk of liver complications
E. I don’t know

Risk Stratification for HBVr



Hwang JP, Lok AS. *Nat Rev Gastroenterol Hepatol*. 2014;11:209-219.

Audience Response

What antiviral prophylaxis treatment would you choose?

A. Interferon
B. Lamivudine
C. Sofosbuvir/ledipasvir
D. Entecavir or tenofovir
E. I don’t know

Audience Response Rationale

What antiviral prophylaxis treatment would you choose?

A. Interferon
B. Lamivudine
C. Sofosbuvir/ledipasvir
D. Entecavir or tenofovir
E. I don’t know

Management Guidelines for HBVr

	HBV Status	Risk Stratification and Management Strategy	Treatment and Duration	Monitoring
AASLD	CHB	• Prophylaxis (PPX)	ETV, TDF, TAF 6-12 mon after IS	Continue up to 12 mon after NA withdrawal (especially if B cell-depleting therapy)
	Resolved HBV	• High-risk therapy (rituximab; SCT): PPX • Other therapies: PPX or on-demand therapy (monitor every 1-3 mon with ALT, HBV DNA, HBsAg)		
AGA	CHB	• High risk (B cell-depleting therapy; anthracycline, moderate-dose CS daily ≥ 4 wks, PPX • Moderate risk (TNF-α therapy, cytokine inhibitor, integrin inhibitor, TKI, low-dose CS): PPS preferred, can consider on-demand therapy	Recommend antiviral with high barrier to resistance 6-12 mon after IS (12 mon if B cell-depleting therapy)	No comment
	Resolved HBV	• High risk (B cell-depleting therapy): PPX • Moderate risk: (TNF-α therapy, cytokine inhibitor, integrin inhibitor, TKI, low-dose CS): PPS preferred, can consider on-demand therapy	Recommend antiviral with high barrier to resistance 6-12 mon after IS (12 mon if B cell-depleting therapy)	
EASL	CHB	• PPX	ETV, TDF, TAF 12 mon after IS, 18 mon if rituximab	Every 3-6 mon during PPX, plus 12 mon after NA withdrawal
	Resolved HBV	• High risk (rituximab for oncological indication; SCT): PPX • Mod or low risk: on-demand therapy (monitor HBsAg and/or HBV DNA every 1-3 mon; treat if +DNA or reverse seroconversion)	ETV, TDF, TAF 18 mon after IS, if rituximab	Continue 12 mon after NA withdrawal

SCT = stem cell transplant; NA = nucleotide analog; IS = immunosuppression; ETV = entecavir; TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide.

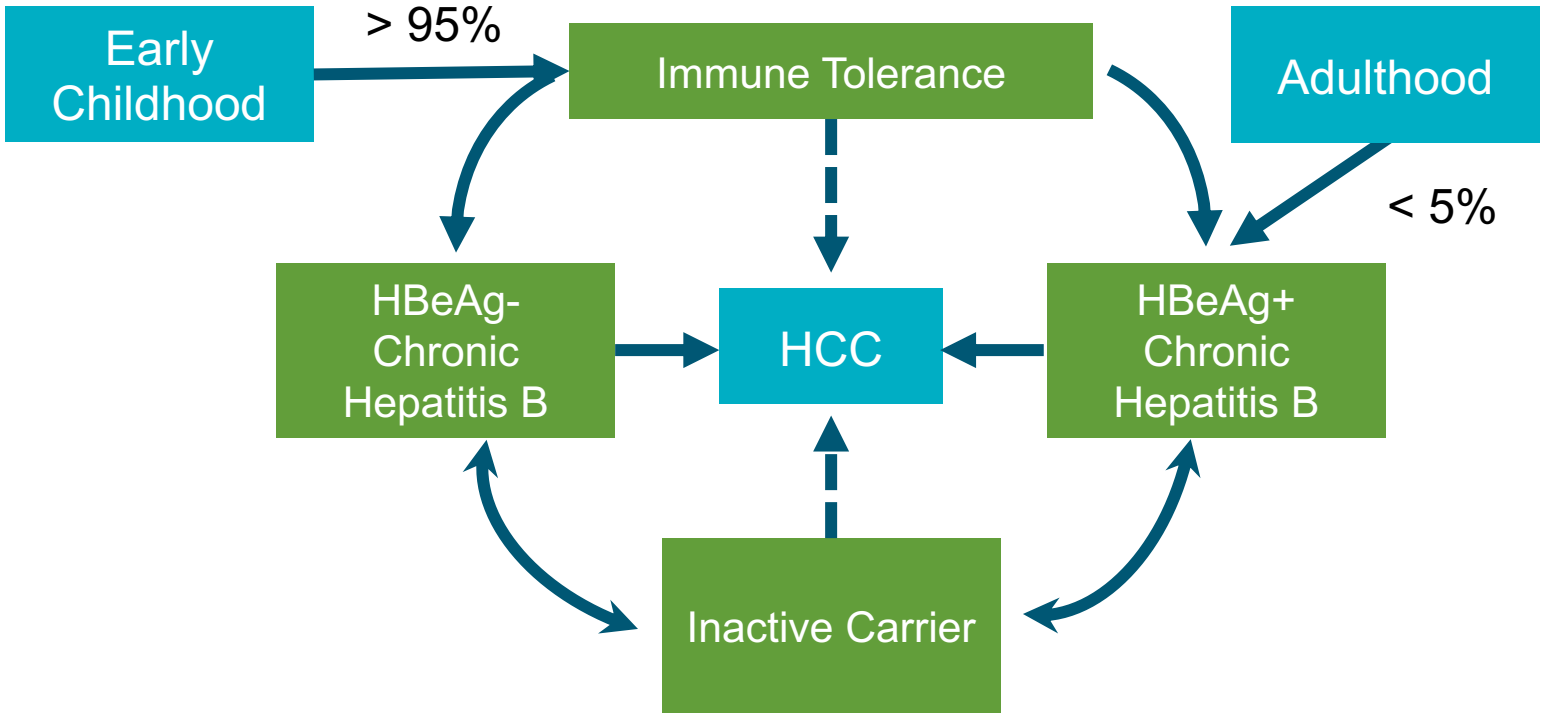
Myint A, et al. *Clin Liver Dis (Hoboken)*. 2020;15(4):162-167.

What About Thomas' Risk for HCC?

- HBV is the leading cause of HCC and deaths in the world[1]
  - 60% in Africa and East Asia
  - 20% in the Western world
- Predictors of HCC in HBV infected individuals[1]
  - HBeAg seropositivity
  - High viral load
  - Genotype C
- Past or resolved HBV infection my lead to resolved HBV infection may still lead to HCC, cirrhotic complications, and liver-related death[2]
- Preexisting cirrhosis found in >80% of individuals with HCC[3]

1. Singal AG, et al. *J Hepatol*. 2020;72(2):250-261.; 2. Wong G, et al. *Am J Gastroenterol*. 2021;116:1274-1283.; 3. Bruix J, et al. *Hepatology*. 2011;53:1020-1022.

Natural History of HBV Infection



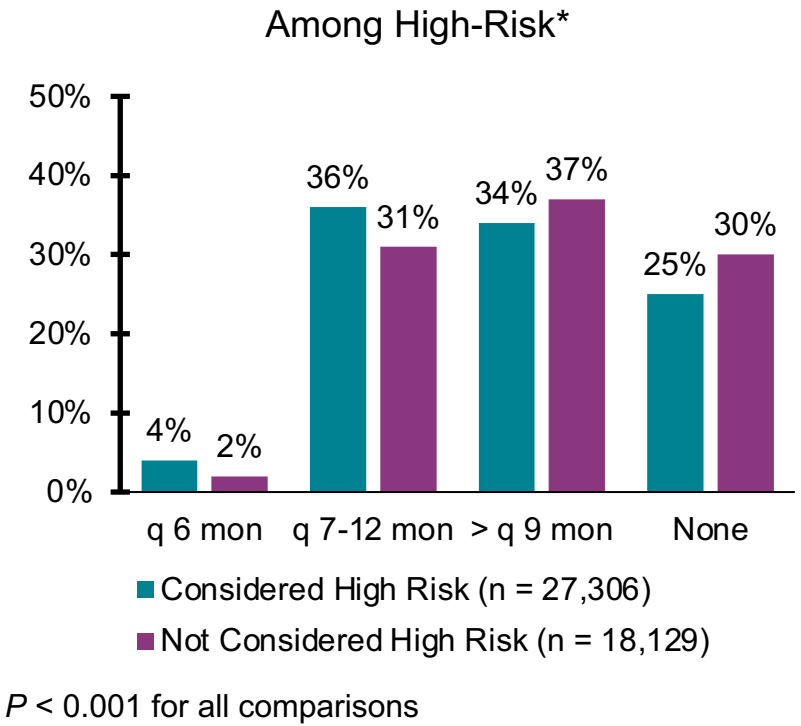
Chen DS, et al. *J Gastroenterol Hep*. 1993;8:470-475. Seef L, et al. *N Engl J Med*. 1987;316:965-970.

Patients at Highest Risk for HCC

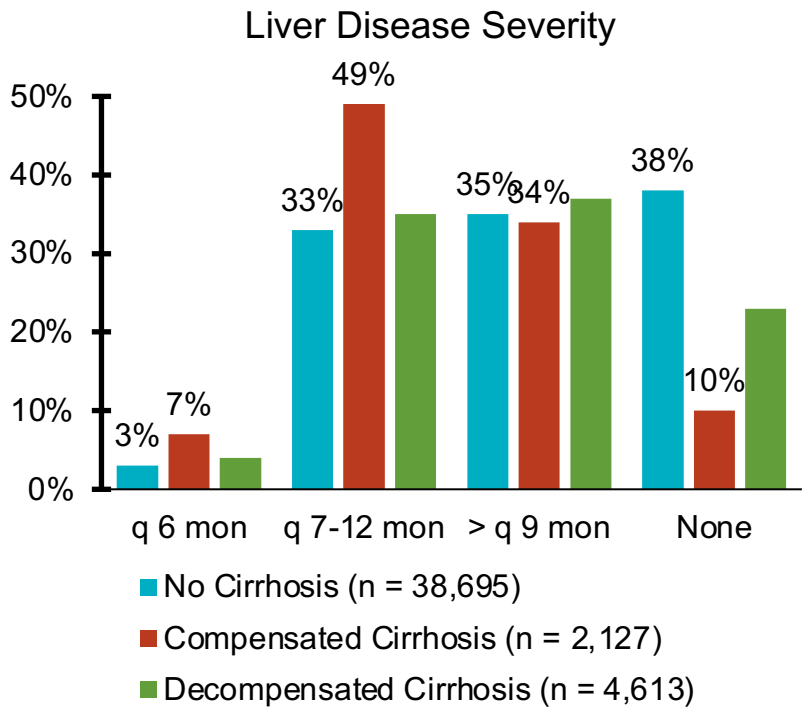
- Asian male HBV carriers > 40 years
- Asian female HBV carriers > 50 years
- HBV carrier with family history of HCC
- African and/or North American Blacks with HBV
- HBV carriers with cirrhosis
- Hepatitis C cirrhosis
- Stage 4 PBC
- Genetic hemochromatosis and cirrhosis
- Alpha-1 antitrypsin deficiency and cirrhosis
- Other cirrhosis

Terrault NA, et al. *Clin Liver Dis (Hoboken).* 2018;12(1):33-34.

Adherence to HCC Surveillance in CHB is Suboptimal



P < 0.001 for all comparisons



*High risk was defined as patient with cirrhosis, males without cirrhosis > 40 yrs, females without cirrhosis > 50 yrs

Tran S, et al. *Am J Gastroenterol*. 2021 Apr 29. doi: 10.14309/ajg.0000000000001271. Online ahead of print.

HCC Monitoring Guidelines

- Liver ultrasound with or without serum alpha-fetoprotein (AFP) every 6 months
  - More frequent monitoring or other imaging modalities such as CT or MRI with and without contrast may be indicated to evaluate new liver lesions
- AASLD recommends not performing surveillance of patients with cirrhosis with Child's class C unless on transplant waiting list, given low anticipated survival

Terrault NA, et al. *Clin Liver Dis (Hoboken).* 2018;12(1):33-34.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Be aware of potential HBVr related to immunosuppressive therapies that are increasingly common across many specialties
- Screen patients for HBV prior to initiation of treatment to reduce HBVr associated morbidity and mortality
- Initiate preferred agents, ETV or TDF, as prophylaxis in appropriate at-risk patients and continue treatment for at minimum 6-12 months following immunosuppressive treatment
- Monitor patients with CHB every 6 months using liver ultrasound with or without serum alpha-fetoprotein

CMEO BriefCase 1

Throwing a Curve Ball at Hepatitis B Serological Tests: Interpreting Results to Guide Next Steps

CMEO BriefCase 2

Taking the Long View: Medical Comorbidities That May Shift Hepatitis B Treatment Decision-Making

www.CMEOutfitters.com/liver-hub

Don’t forget to complete the post-test and evaluation!

You can download your certificate from the website