HEPATITIS B ONLINE

Isolated Hepatitis B Core Antibody

H. Nina Kim, MD MSc
Professor of Medicine
University of Washington

Last Updated: October 7, 2022

Disclosures

H. Nina Kim, MD MSc

Gilead Sciences provides program funding to my institution

Topics

- Virology and definition
- When isolated anti-HBc is encountered
- Clinical significance
  - Occult HBV infection
  - HBV reactivation
- HBV immunization

Hepatitis B Virus: Key Structures

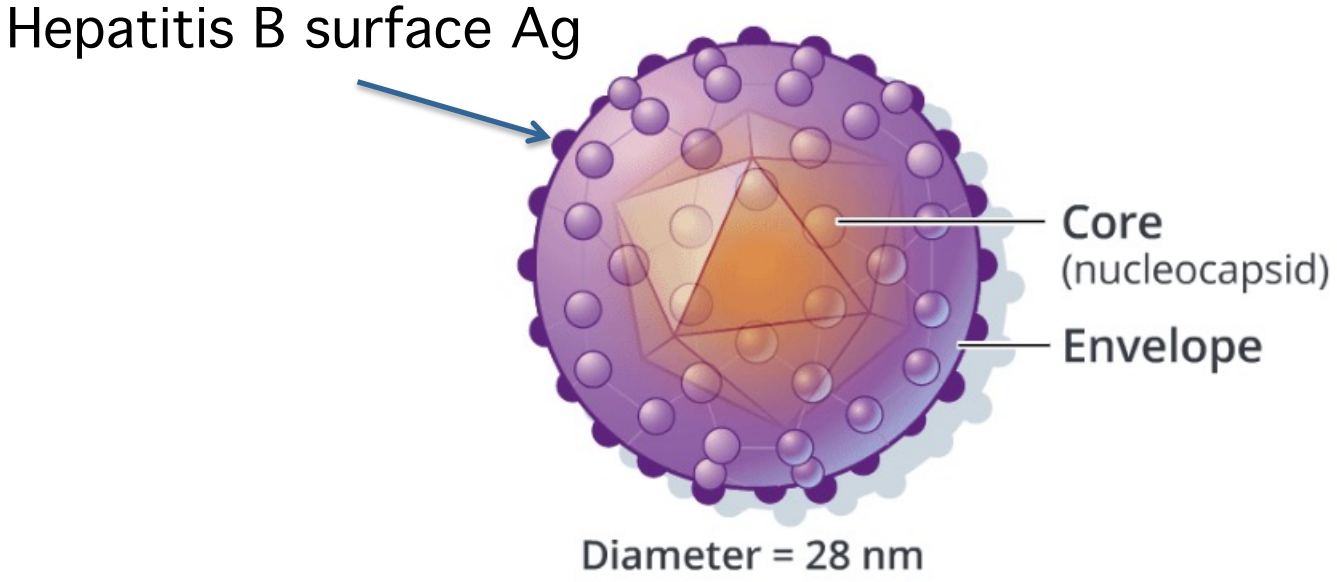

Image Credit: Cognition Studios, Inc.

Hepatitis B Virus: E antigen and Core antigen

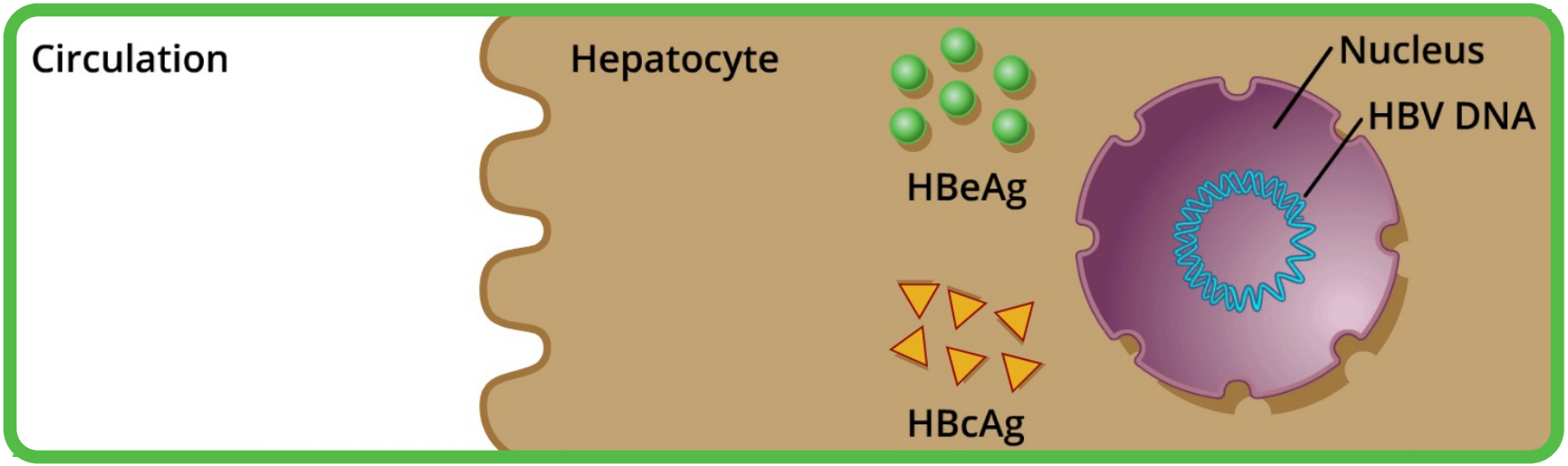

Image Credit: Cognition Studios, Inc.

Hepatitis B Virus: E antigen and Core antigen

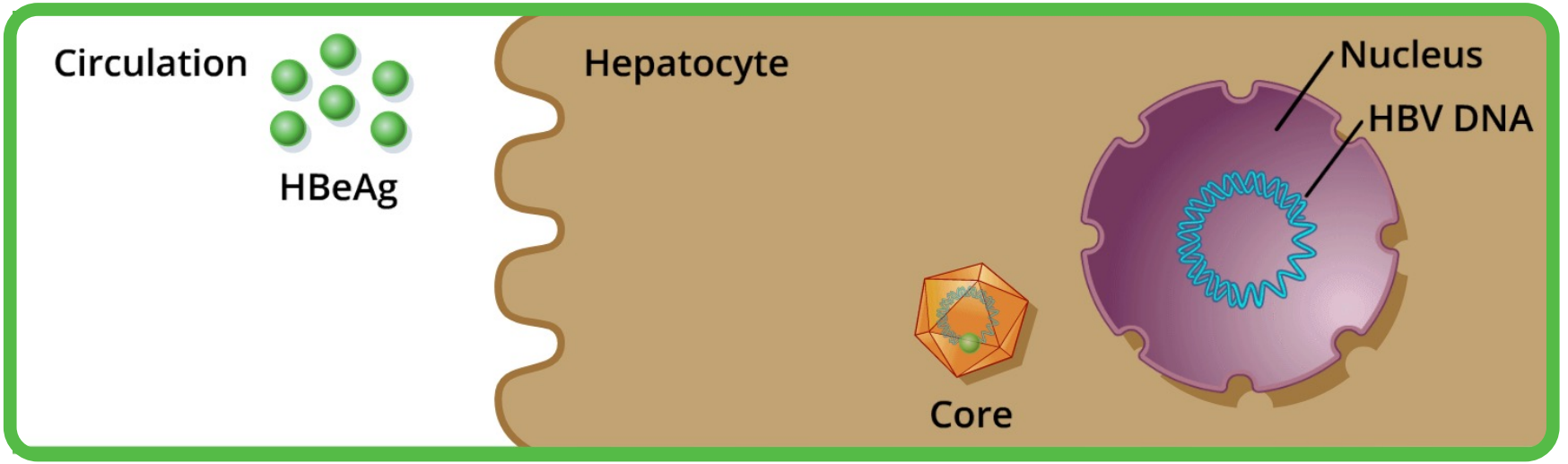

Image Credit: Cognition Studios, Inc.

Natural History of Acute Resolved HBV

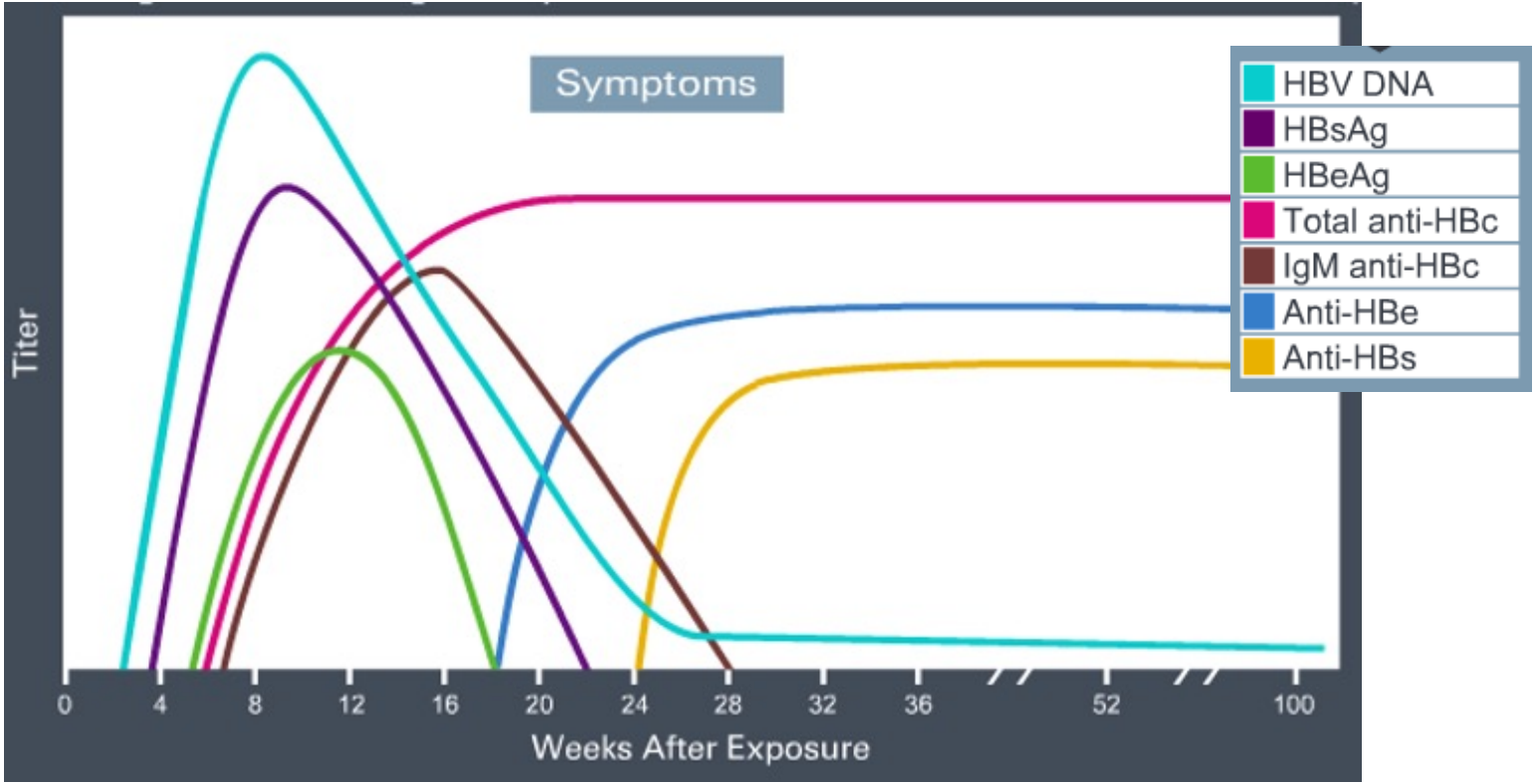

Image Credit: Cognition Studios, Inc.

Core Antibody

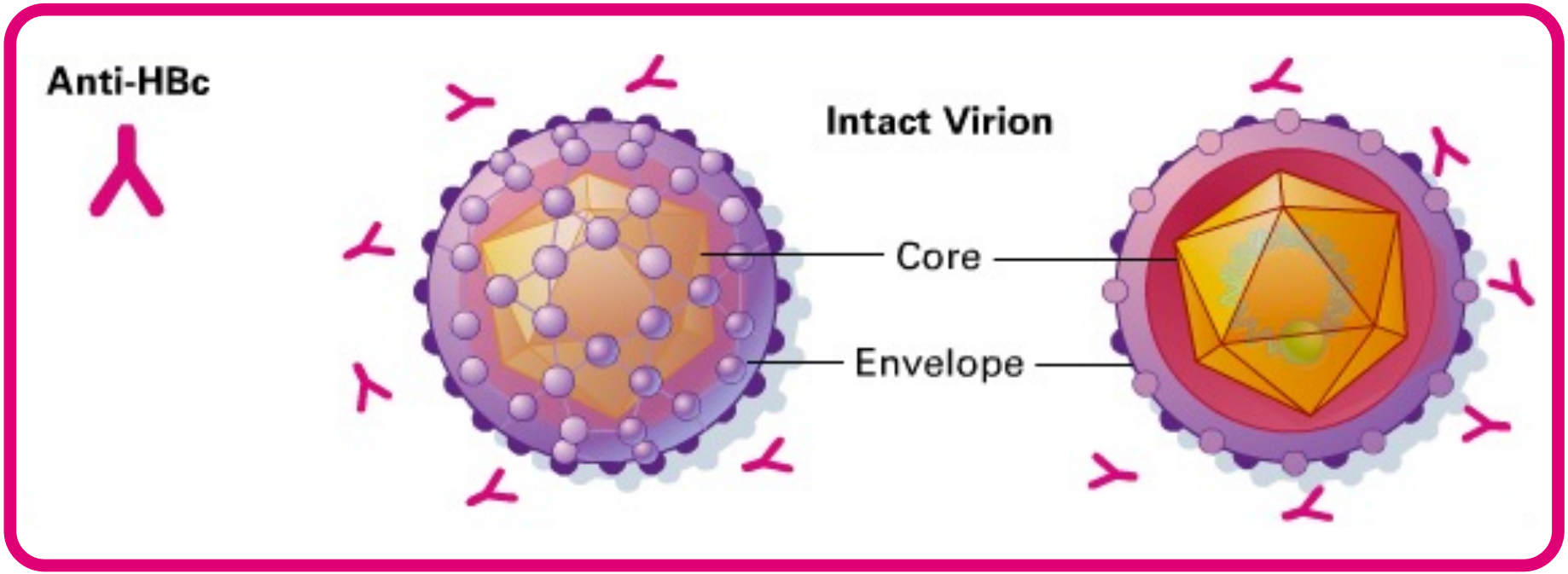

Image Credit: Cognition Studios, Inc.

Isolated Hepatitis B Core Antibody

- Definition: **Anti-HB core Ab(+)** but anti-HBs and HBs antigen negative
- Common profile
  - 20-45% in persons with HIV and 5-31% in persons without
- **Factors** associated with isolated core Ab:
  - Chronic hepatitis C infection
  - Injection drug use; multiple sex partners
  - Older age
  - HIV: CD4 count <100 cells/mm^3, HIV viremia

Source: Chang et al, Current HIV/AIDS Reports.2018:15;172–81.

Isolated Hep B Core: Four Scenarios

- Window phase of acute infection
- Resolved HBV infection with waning anti-HBs
- Occult HBV with loss of HBsAg
- False positive

Isolated Hep B Core: Four Scenarios

- **Window phase of acute infection**
- Resolved HBV infection with waning anti-HBs
- Occult HBV with loss of HBsAg
- False positive

Isolated Hep B Core: Four Scenarios

- Window phase of acute infection
- **Resolved HBV infection with waning anti-HBs**
- Occult HBV with loss of HBsAg
- False positive

Isolated Hep B Core: Four Scenarios

- Window phase of acute infection
- Resolved HBV infection with waning anti-HBs
- **Occult HBV with loss of HBsAg**
- False positive

Isolated Hep B Core: Four Scenarios

- Window phase of acute infection
- Resolved HBV infection with waning anti-HBs
- Occult HBV with loss of HBsAg
- **False positive**

Isolated Hep B Core: Clinical Significance

- Stable pattern over time in most individuals
  - Still present if retested
  - If changes → transition to natural immunity (+anti-HBc and +anti-HBs)
  - Transition to chronic hep B (gain/loss of HBsAg) is rare
- Not usually associated with:
  - ALT/AST elevations
  - Liver stiffness by FibroScan
  - Cirrhosis or HCC
  - Secondary transmission

Source Witt MD, et al. Clin Infect Dis. 2013;56:606–12.

Isolated Hepatitis B Core Antibody
Occult Hepatitis B

- Isolated core Ab (+), negative surface Ag with (+) HBV DNA level
- Prevalence variable (geography, population & assays differ)
  - Estimated prevalence ~2-41% among isolated core pts
  - True prevalence may be underestimated due to
    - ✓Cross-sectional nature of many studies
    - ✓Fact that patients may be on HBV-active antivirals (HIV cohorts)
- HBV viral levels detected typically low (<1000 IU/mL range) but also quite variable.

Source:
Wu T, et al. Am J Gastroenterol. 2017;112:1780–8.
Chang JJ, et al. Current HIV/AIDS Reports. 2018;15:172–81.

ORIGINAL RESEARCH

Annals of Internal Medicine

Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus: A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System

Susan J. Bersoff-Matcha, MD; Kelly Cao, PharmD; Mihaela Jason, PharmD; Adebola Ajao, PhD; S. Christopher Jones, PharmD, MS, MPH; Tamra Meyer, PhD, MPH; and Allen Brinker, MD, MS

Background: Direct-acting antiviral agents (DAAs) are used increasingly to treat hepatitis C virus (HCV) infection. Reports were published recently on hepatitis B virus (HBV) reactivation (HBV-R) in patients with HBV–HCV co-infection. Hepatitis B virus reactivation, defined as an abrupt increase in HBV replication in patients with inactive or resolved HBV infection, may result in clinically significant hepatitis.

Objective: To assess whether HBV-R is a safety concern in patients receiving HCV DAAs.

Design: Descriptive case series.

Setting: U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

Patients: 29 patients with HBV-R receiving HCV DAAs.

Measurements: Clinical and laboratory data.

Results: The FDA identified 29 unique reports of HBV-R in patients receiving DAAs from 22 November 2013 to 15 October 2016. Two cases resulted in death and 1 case in liver transplantation. Patients in whom HBV-R developed were heterogeneous regarding HCV genotype, DAAs received, and baseline HBV characteristics. At baseline, 9 patients had a detectable HBV viral load, 7 had positive results on hepatitis B surface antigen (HBsAg) testing and had an undetectable HBV viral load, and 3 had negative results on HBsAg testing and had an undetectable HBV viral load. For the remaining 10 patients, data points were not reported or the data were uninterpretable. Despite provider knowledge of baseline HBV, HBV-R diagnosis and treatment were delayed in 7 cases and possibly 7 others.

Limitations: The quality of information varied among reports. Because reporting is voluntary, HBV-R associated with DAAs likely is underreported.

Conclusion: Hepatitis B virus reactivation is a newly identified safety concern in patients with HBV–HCV co-infection treated with DAAs. Patients with a history of HBV require clinical monitoring while receiving DAA therapy. Studies would help determine the risk factors for HBV-R, define monitoring frequency, and identify patients who may benefit from HBV prophylaxis and treatment. DAAs remain a safe and highly effective treatment for the management of HCV infection.

Primary Funding Source: None.

Ann Intern Med. 2017;166:792-798. doi:10.7326/M17-0377 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 25 April 2017.

HEPATITIS B ONLINE

Isolated anti-HBc in DAA Therapy

- HBV reactivation with DAA therapy much rarer than w/ chronic hep B
  - Estimated incidence 14% among chronic HBV (95% CI 8-22).
  - Only 3 cases of occult HBV reactivating with DAAs
- Insufficient data to provide clear recommendations
- AASLD/IDSA HCV guidance on isolated core:

> "However, the possibility of HBV reactivation should be considered in these patients in the event of an unexplained increase in liver aminotransferase levels during and/or after completion of DAA therapy."

Source:
Wu T, et al. Am J Gastroenterol. 2017;112:1780–8.
Belperio PS, et al. Hepatology 2017;66:27–36.
Chen G, et al. Hepatology. 2017;66:13–26.
AASLD/IDSA HCV Guidance. Accessed at www.hcvguidelines.org

original article

Annals of Oncology 22: 1170–1180, 2011
doi:10.1093/annonc/mdq583
Published online 29 November 2010

Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports

A. M. Evens[1,2]*, B. D. Jovanovic[1,3], Y.-C. Su[4], D. W. Raisch[5], D. Ganger[1,6], S. M. Belknap[1,7], M.-S. Dai[8], B.-C. C. Chiu[9], B. Fintel[1,7], Y. Cheng[5], S.-S. Chuang[10], M.-Y. Lee[11], T.-Y. Chen[12], S.-F. Lin[13] & C.-Y. Kuo[14]

[1]*Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, USA;* [2]*Division of Hematology/Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University;* [3]*Department of Preventive Medicine;* [4]*Division of Oncology, Dalin Tzu-Chi General Hospital, Chiayi, Taiwan;* [5]*Veterans Administration Cooperative Studies Program College of Pharmacy, University of New Mexico, Albuquerque, USA;* [6]*Division of Hepatology;* [7]*Department of Internal Medicine;* [8]*Division of Hematology/Oncology, Tri-Service General Hospital, Taipei, Taiwan;* [9]*Department of Health Studies, Division of Epidemiology, The University of Chicago, Chicago, USA;* [10]*Department of Pathology, Chi-Mei Medical Center, Tainan and Taipei Medical University, Taipei;* [11]*Division of Oncology, Chia-Yi Christian Hospital, Chiayi;* [12]*Division of Oncology, National Cheng Kung University Hospital, Tainan;* [13]*Faculty of Medicine and Division of Hematology & Oncology, Kaohsiung Medical University and Hospital, Kaohsiung;* [14]*Division of Hematology/Oncology, Chang Gung Memorial Hospital–Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan*

Received 6 July 2010; revised 16 August 2010; accepted 19 August 2010

Background: Rituximab has been associated with hepatitis B virus reactivation (HBV-R). However, the characteristics and scope of this association remain largely undefined.

Methods: We completed a comprehensive literature search of all published rituximab-associated HBV-R cases and from the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) MedWatch database. Literature and FDA cases were compared for completeness, and a meta-analysis was completed.

Results: One hundred and eighty-three unique cases of rituximab-associated HBV-R were identified from the literature ($n = 27$ case reports, $n = 156$ case series). The time from last rituximab to reactivation was 3 months (range 0–12), although 29% occurred >6 months after last rituximab. Within FDA data ($n = 118$ cases), there was a strong signal for rituximab-associated HBV-R [proportional reporting ratio = 28.5, 95% confidence interval (CI) 23.9–34.1; Empiric Bayes Geometric

Hepatitis B Online

HBV Immunization for Isolated Core Ab

- No evidence to support routine “boosting”
  - Remember: most of these individuals are already infected with HBV
  - Most have waned anti-HBs but this does not mean they won’t mount a protective immune response to future exposure
  - Occult HBV: benefit of immunization is not clear
- Immunization should be reserved for
  - False positive anti-HBc (no HBV risk factors, not from HBV endemic region)
  - People with HIV

Source: Terrault N, et al. Hepatol. 2018;67:1560–99.
Weng M, et. al. MMWR Morb Mortal Wkly Rep 2022;71:477–483.

Take Aways: Isolated Hep B Core Ab

- The core antibody is most sensitive marker of prior exposure to the hepatitis B virus.
- This does not necessarily indicate active infection or immunity but most are likely to be immune (with waned anti-HBs).
- Consider occult HBV and the possibility of HBV reactivation
  - Hepatitis C treatment with DAAs or B cell depleting immunologic therapy
  - Esp. if individual is from HBV-endemic region (e.g. Asia or Africa)
- Immunize if they meet criteria for false positive or have HIV.

Hepatitis B Online

A free educational website from the
University of Washington Infectious Diseases Education & Assessment (IDEA) program

Contributors

Funded by
Centers for Disease Control and Prevention (CDC)

Course Modules

Quick Access to Course Information
Self Study with Progress Tracker
Free CME and CNE/CE

Start the Self-Study Modules »

Hepatitis B Virus

HBV Epidemiology
Reviews United States and global HBV incidence and prevalence, populations at risk for HBV acquisition, and the clinical and laboratory criteria for HBV case definitions.

Quick Reference ›
Rapidly access info about Epidemiology

Self-Study CNE/CME
Track progress and receive CE credit

HBV Screening and Diagnosis
Details the groups considered at priority for HBV testing, the recommended screening and diagnostic tests, and how to interpret HBV diagnostic test results.

Quick Reference ›
Rapidly access info about Screening and Diagnosis

Self-Study CNE/CME
Track progress and receive CE credit

HBV Immunizations
Identifies indications for HBV vaccine, describes dosing schedules and administration of vaccines, and management of vaccine nonresponders

Quick Reference ›
Rapidly access info about Immunization

Self-Study CNE/CME
Track progress and receive CE credit

Acknowledgments

Hepatitis B Online is funded by a cooperative agreement from the Centers for Disease Control and Prevention (CDC-RFA-PS21-2105). This project is led by the University of Washington Infectious Diseases Education and Assessment (IDEA) Program.

HEPATITIS C ONLINE

HEPATITIS B ONLINE

IDEA INFECTIOUS DISEASES EDUCATION & ASSESSMENT

The content in this presentation is that of the author(s) and does not necessarily represent the official position of the Centers for Disease Control and Prevention.