Hepatitis B Reactivation

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Definition of HBV Reactivation

• Loss of HBV immune control in a patient with inactive or resolved HBV infection

• Reappearance or increase in viral replication with liver damage occurring during and/or following immune reconstitution
  – Sudden and rapid increase in HBV-DNA level
HBV Reactivation

- Increasing in incidence
- Preventable with education

Loomba, Liang. Gastro 2017;152:1297-1309
Clinical Range of HBV Reactivation

- Reappearance of HBsAg / HBeAg
- ALT increase
- Ranges from subclinical to severe to liver failure and death
Do You Ever Really Get Rid of HBV?

- Immune control—not clearance
- “Resolved HBV” a misnomer—still HBV DNA in liver

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Along Comes Immune Suppression

- Immune control can be lost
- Immune-mediated liver damage with immune reconstitution

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Early Reports of Reactivation: Hematologic Malignancy

100 patients with NHL undergoing CHOP;
27 HBsAg positive

Steroids Increase Risk of HBV Reactivation

50 patients with NHL who were HBsAg positive randomized to epirubicin, cyclophosphamide and etoposide (ACE) ± prednisolone (P)

Prednisolone increased risk and severity of HBV reactivation but trend toward improved NHL outcome

HBV Reactivation: Categories

• HBsAg positive with or without detectable HBVDNA
• HBsAg negative with detectable HBcAb
Onset of HBV Reactivation

• May occur as early as 2 weeks of onset of chemotherapy/ immunosuppression
• May occur up to a year after cessation of chemotherapy / immunosuppression
Risk Factors of HBV Reactivation

- Host factors
- Virological factors
- Type and degree of immunosuppression

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Risk Factors of HBV Reactivation: Host Factors

- Male sex
- Older age
- Presence of cirrhosis
- Disease needing immunosuppression
  - Lymphoma
  - Leukemia

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Risk Factors of HBV Reactivation:  
Virological Factors

• High baseline HBV-DNA
• HBeAg positive
• Non-A genotype
• Co-infection with HCV

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Risk Factors for Reactivation:
Type and Degree of Immunosuppression

• High risk  \( \geq 10\% \) risk of reactivation
• Moderate risk  1-10\% risk of reactivation
• Low risk  \(< 1\% \) risk of reactivation
HBV life cycle and mechanisms associated with HBV reactivation
Risk of HBV Reactivation Varies with Immunosuppressive Agent

- **Anti-TNF**
  - (Infliximab, adalimumab, etanercept)

- **Anti-Metabolite**
  - (Methotrexate)

- **Purine Analogue**
  - (Azathioprine/6MP)

- **Steroids**
  - (Prednisone, budesonide)

- **Other**
  - (Rituximab, cyclosporine)
Rituximab: A Particular Problem

- Monoclonal antibody against CD20
- Reduces B cell numbers and antibody levels
- NHL, CLL, RA
  - Regularly used as part of CHOP-R, EPOCH-R
- Increased risk of HBV reactivation, including HBsAg-negative patients, HBcAb + only patients
- FDA black box warning issued in Sept 2013
  - 106 fatal cases of HBV reactivation in patients treated with rituximab
  - Reactivation occurred 2-12 months after last dose of drug
AGA Recommendations for Prevention and Treatment of HBV Reactivation during Immunosuppressive Drug Therapy: **High Risk Groups**

- **HBsAg+/HBcAb+**
  - Or
  - **HBsAg-/HBcAb+**
    - B-cell depleting agents (rituximab, ofatumumab)
    - Anthracycline Derivatives (doxorubicin, epirubicin)
    - Prednisone > 10 mg a day for > 4 weeks

- **HBsAg+/HBcAb+**
  - Suggest anti-viral prophylaxis for at least 12 months after discontinuation of immunosuppressive therapy
  - Suggest anti-viral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy

AGA Recommendations for Prevention and Treatment of HBV Reactivation during Immunosuppressive Drug Therapy: **Moderate Risk Groups**

- HBsAg+ / HBcAb+
- or HBsAg- / HBcAb+

**TNF inhibitors** (etanercept, adalimumab, infliximab)

**Tyrosine kinase inhibitors** (imatinib, nilotinib)

**Cytokine or integrin inhibitors** (abatacept, ustekinumab, natalizumab, vedolizumab)

Suggest anti-viral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy

AGA Recommendations for Prevention and Treatment of HBV Reactivation during Immunosuppressive Drug Therapy:  Moderate Risk Groups

**HBsAg+/HBcAb+**
- Low dose prednisone (<10 mg daily for ≥ 4 weeks)

**HBsAg-/HBcAb+**
- Prednisone (>10 mg daily for ≥ 4 weeks)
- Anthracycline derivatives (Doxorubicin, epirubicin)

Suggest anti-viral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy

AGA Recommendations for Prevention and Treatment of HBV Reactivation during Immunosuppressive Drug Therapy: **Low Risk Groups**

- **HBsAg+/HBcAb+ or HBsAg-/HBcAb+**
  - Traditional immunosuppressive agents (Azathioprine, 6-MP, MTX)
  - Intra-articular steroids or any dose oral steroids ≤ 1 weeks

- **HBsAg-/HBcAb+**
  - Low dose prednisone (<10 mg daily for ≥ 4 weeks)

No use of anti-viral prophylaxis

PREVENTION OF HEPATITIS B REACTIVATION
What Tests Should I Screen With?

• HBsAg and HBcAb in all individuals undergoing immunosuppression
• Check HBV DNA in HBsAg + patients
• Consider HBsAb, but not mandatory
  – Risk is not consistently less if HBsAb+
  – Does not alter management

LAM Reduces Risk of HBV-Reactivation

HBsAg+ patients with lymphoma treated with high-dose chemotherapy randomized to preemptive versus on-demand LAM

Survival Free from Hepatitis Due to HBV Reactivation

Week

Patients at risk, n
Preemptive LAM  15  12  10  9  6
On-demand LAM  15  13  10  4  2

P = .002 by log-rank test

Prophylaxis of HBV Reactivation With Tenofovir

- Prospective, open-label study (n=69)
  - HBeAg-positive and -negative patients
  - **HBV DNA undetectable before starting rituximab for hematologic malignancies**
- Preliminary analysis of first 12 months in 30 of 69 patients enrolled
- Study arms (18 months)
  - Tenofovir DF
  - Observation

**HBV Reactivation (12-Month Preliminary Analysis)**

- **Tenofovir DF (n=18)**
  - 16.7%
- **Observation (n=12)**
  - 0%

*P*=0.152
Treatment Regimens for Prevention of HBV Reactivation

- Entecavir 0.5 mg/day
- Tenofovir disoproxil 300 mg /day
- Tenofovir alafenamide 25 mg/day
Timing of Initiation of Antiviral Therapy

• Ideally before or together with chemotherapy
  • 2 weeks prior to chemotherapy is ideal
    – Do not delay start of chemotherapy

• Monitor for withdrawal flares with monthly HBV DNA and ALT

Who Should Be Screened Prior to Chemotherapy?

• AASLD recommends screening all patients before initiation of immunosuppressive, cytotoxic, or immunomodulatory therapy

• CDC, EASL, ASCO have the same recommendation

Hepatitis C Therapy

REACTIVATION
Safety WARNING: HBV Reactivation and DAAs
October, 2016

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

Safety Announcement

[10-04-2016] The U.S. Food and Drug Administration (FDA) is warning about the risk of hepatitis B virus (HBV) becoming an active infection again in any patient who has a current or previous infection with HBV and is treated with certain direct-acting antiviral (DAA) medicines for hepatitis C virus. In a few cases, HBV reactivation in patients treated with DAA medicines resulted in serious liver problems or death.
Reactivation of Hepatitis B

- Patients with prior, resolved, or active HBV infection are at risk of reactivation on DAA therapy
- FDA issued black box warning in 2016
  - 29 reactivations reported since 2013
    - 2 died, 1 required liver transplant
- Mechanism of reactivation unknown

Suggested Monitoring for HBV Reactivation During DAA for HCV

Test HBV Markers in All DAA Candidates:
1) HBsAg, 2) Anti-HBc, 3) Anti-HBs

HBV Markers NEGATIVE

HBsAg POSITIVE

HBV DNA Detectable

Meets AASLD criteria for initiation of HBV therapy

Treat with HBV drug

HBV DNA Low or UD

Initiate prophylactic antiviral therapy until 12 weeks after DAA completion

HBsAg NEGATIVE anti-HBc POSITIVE (± anti-HBs)

Specific HBV monitoring not required unless change in liver enzymes or clinical status

HBV Markers NEGATIVE

VACCINATE

HBVr Standard Definition:
- Marked increased in HBV DNA (≥2 log increase from baseline levels) OR
- New appearance of HBV DNA to a level of > 100 IU/mL in a person with previously stable or undetectable levels.

Monitor for HBV:
- Check HBV DNA + LFTs q2 weeks during & after DAA therapy
- Start HBV Therapy if:
  - HBV DNA >10-fold above baseline OR
  - HBV DNA >1000 IU/mL

Adapted from AASLD Guidelines

Lieber and Fried, 2017
HBV Reactivation: Summary

• All patients to be started on immunosuppression/chemotherapy/ DAA therapy for HCV should be screened for HBV.
• Initial screening tests are **HBsAg** and **HBcAb**.
• Prophylactic therapy indicated with tenofovir or entecavir in moderate or high risk patients.
• **HBV reactivation is preventable**.