Hepatitis B
Diagnosis and Management
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COI

- Spouse works for Hoffmann-La Roche
HBV is a life long, dynamic disease

- Changes over time
- Risk of end stage liver disease and cancer increases with ongoing inflammation and viremia in adults
- Fibrosis can be reversible
- Drugs can decrease fibrosis progression
- HBV can be controlled but not cured
- Reactivation can occur even in those who have lost HBsAg
Prevalence of HBV in HIV-Positive and negative patients

Estimated Number of Persons Infected Worldwide, in Millions

- About 5% to 10% of anti-HCV-antibody–positive patients are HBsAg-positive
- Hepatitis C superinfection of chronic HBsAg carriers is common in HBV endemic regions, such as Southeast Asia

Geographic Distribution of HBV Genotypes

Greenland:
- A, B, D

- Ae, Bj, C, D, F

- B, A/Bj

- B, C, A, D

- G

- F₁, H

- H

- F₂

- Aa

- B, A/Bj

- Ba

- B

- B₂

- B₃

- Bj

- C

- D

- A, B, D

- A, B, D

- Ba

- B

- B₂

- B₃

- Bj

- C
HBsAg
DNA
cAg

Dane Particle
Infectious virion

HBsAg
HBeAg

Subviral particles
Hepatitis B Virus
HBV Serologic Markers

**HBsAg**
- Acute or chronic infection
- First serologic marker to appear
- Infection considered chronic if persistent for > 6 months

**HBeAg**
- Indicates active replication of virus
- Absent if inactive or mutations develop

**Anti-HBc total (HBcAb total)**
- Present in infection (IgM in acute infection)
- Present in past exposure to HBV
- May occur alone when anti-HBs wanes

**Anti-HBs**
- Recovery from HBV with anti-HBc
- Detectable alone after immunity conferred by HBV vaccination
- Occasionally seen in chronic carriers with HBsAg & anti-HBc

**Anti-HBe**
- Generally indicates virus is no longer replicating
- Present in those with HBeAg mutations who have active disease

## What to do with results?

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBsAb</th>
<th>HBcAb</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• +</td>
<td>-</td>
<td>+</td>
<td>refer to care</td>
</tr>
<tr>
<td>• -</td>
<td>+</td>
<td>+</td>
<td>past infection*</td>
</tr>
<tr>
<td>• -</td>
<td>-</td>
<td>-</td>
<td>vaccinate</td>
</tr>
<tr>
<td>• -</td>
<td>+</td>
<td>-</td>
<td>immune (vaccinated)</td>
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</tbody>
</table>

* latent infection important if immune compromised or chemo BRM
HBV Control

• **Inflammatory**: normalize serum ALT, biopsy
• **Virologic**: decrease HBV DNA
• **Immune**: seroconversion
  – HBeAg to anti-HBe
  – HBsAg to anti-HBs
• HBV as of 2018 not “cured” but controlled
Who to treat

• Those with inflammation and fibrosis
  – Elevated ALT and
  – Elevated HBV DNA

• If not clear – Liver biopsy
# EASL Guidelines 2017

<table>
<thead>
<tr>
<th></th>
<th>HBeAg positive</th>
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<tbody>
<tr>
<td><strong>Chronic infection</strong></td>
<td></td>
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<tr>
<td>HBsAg</td>
<td>High</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>&gt;10^7 IU/ml</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
</tr>
<tr>
<td>Liver disease</td>
<td>None/minimal</td>
</tr>
<tr>
<td>Old terminology</td>
<td>Immune tolerant</td>
</tr>
<tr>
<td><strong>Chronic hepatitis</strong></td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>High/intermediate</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Positive</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>10^4-10^7 IU/ml</td>
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<tr>
<td>ALT</td>
<td>Elevated</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Moderate/severe</td>
</tr>
<tr>
<td>Old terminology</td>
<td>Immune reactive HBeAg positive</td>
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### EASL Guidelines 2017

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<tr>
<th>HBsAg</th>
<th>Chronic infection</th>
<th>Chronic hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Intermediate</td>
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<tr>
<td>HBeAg</td>
<td>Negative</td>
<td>Negative</td>
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<tr>
<td>HBV DNA</td>
<td>&lt;2,000 IU/ml</td>
<td>&gt;2,000 IU/ml</td>
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<tr>
<td>ALT</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Liver disease</td>
<td>None</td>
<td>Moderate/severe</td>
</tr>
<tr>
<td>Old terminology</td>
<td>Inactive carrier</td>
<td>HBeAg negative chronic hepatitis</td>
</tr>
</tbody>
</table>

J Hep 2017
Monitoring HBV monoinfection

- Serum ALT- check every 3 months at first
  - If normal for one year, follow labs every 6 months
    - (normal ALT <20 for women, <=30 for men)
    - Older patients may have cirrhosis with normal serum ALT
- HBV DNA
  - If low monitor
  - If elevated consider need for therapy
- Over age 40 or family history monitor for HCC
Who should be treated

- Chronic hepatitis (elevated ALT and HBV DNA)
- Cirrhotics- any level ALT, detectable DNA
- HCC
- HIV
- On Chemotherapy or biologics
- Pregnancy
  - 3rd trimester if HBV DNA >200,000 IU/mL
Approved HBV treatments 2018

• Interferon alfa-2b – 1991
• Lamivudine – 1998
• Adefovir – 2002
• Entecavir – 2005
• Peginterferon alfa-2a – 2005
• Telbivudine – 2006
• Tenofovir Dipivoxil – 2008
• Tenofovir alafenamide – 2017
Long-term Entecavir Treatment Improves Liver Histology and Fibrosis


Coprimary Endpoints

Histologic improvement

- Wk 48: 73%
- Long-term biopsy >3y: 96%

Fibrosis improvement

- Wk 48: 32%
- Long-term biopsy >3y: 88%

Patients (%)
Undetectable HBV DNA Over Time in HBeAg Negative Patients

Not head-to-head trials; different patient populations and trial designs

Extended Treatment With Nucleos(t)ide Analogues vs 1 Yr Peginterferon Treatment

<table>
<thead>
<tr>
<th></th>
<th>1 Yr</th>
<th>2 Yrs</th>
<th>3 Yrs</th>
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<tbody>
<tr>
<td>Entecavir</td>
<td>93</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>90</td>
<td>63</td>
<td>100*</td>
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<tr>
<td>Peginterferon</td>
<td>NA</td>
<td>15</td>
<td>16</td>
</tr>
</tbody>
</table>

*Single center study.

HBsAg Loss Over Time in HBeAg Positive Patients

Not head-to-head trials; different patient populations and trial designs

Extended Treatment With Nucleos(t)ide Analogues* vs 1 Yr Peginterferon Treatment

*With sustained undetectable HBV DNA.

HBsAg Loss Over Time in HBeAg Negative Patients

Not head-to-head trials; different patient populations and trial designs

Extended Treatment With Nucleos(t)ide Analogues* Vs 1 Yr Peginterferon Treatment

*With sustained undetectable HBV DNA.

Types of HBV cure

**Functional Cure - clinical resolution**

Sustained, off drug:
- No inflammation: ALT and liver biopsy
- HBsAg loss
- Anti-HBs gain

**Complete cure - virological cure**
- All of above plus
- Loss of cccDNA in liver

**Inactive state - an interim goal?**
- No inflammation: ALT and liver biopsy
- HBV DNA low or u/d
- HBsAg positive
Viral Life Cycle

Entry → ER → Budding → Recycling → Plus strand synthesis → Minus strand synthesis → Reverse transcriptase → HBsAg pos

Nucleus

Transcription → Host RNA pol → cccDNA → Repair

S, C, P, e synthesis → Translation

RNA packaging (encapsidation)
Viral Life Cycle- “latent or recovered” HBV

Immune system considers this “recovered”
BUT cccDNA is template for viral replication

HBsAg neg
Anti-HBs
Anti-HBc

Nucleus
cccDNA
ER
Patients on Immunosuppressive Therapy

There is a high rate of HBV reactivation in immunosuppressed patients:
- During chemotherapy
- In HIV patients after immune reconstitution
- After organ transplant and stem cell transplant
- With biologic response modifiers: Rituximab (anti-CD20), TNF-α inhibitors

- Rituximab/ stem cell transplant the most potent reactivator of HBV
- Prophylax if anti-HBc without HBsAg

All patients should be tested prior to chemotherapy for:

HBsAg, anti-HBs and anti-HBc

Patients on Immunosuppressive Therapy

- All patients who are to receive immunosuppressive therapy should be tested for HBsAg and anti-HBc and anti-HBs
  - If HBsAg positive, initiate antiviral therapy before IS
  - If anti-HBc positive but HBsAg negative:
    - Anti-HBV therapy should be administered preemptively for rituximab or stem cell transplant
    - Consider preemptive anti-HBV therapy for other forms of chemotherapy or close monitoring of HBV DNA if anti-HBV therapy not given

HCC and HBV

• Increased risk of progression/HCC shown in:
  – male sex
  – younger age of infection
  – Excess alcohol consumption, NAFLD
  – High hepatitis B DNA levels (over age 40 years)
  – Co-infections with HIV, HCV and HDV
  – Hepatitis B virus genotype C, Aa

• Screen with 6 monthly ultrasound and AFP
  – If lesion CT or MRI to determine if HCC

HCC - RADIOLOGIC CHARACTERISTICS
QUAD-PHASE CT OF THE ABDOMEN

Arterial Phase Enhancement

Portal Venous phase “washout”
Baseline HBV DNA and HCC

REVEAL study cohort 3,582

Age 45, Male 61%, ALT>45 6%, HBeAg-positive 15%

Relative Risk (95% CI)

- $10^6$: 14.89% (10.7, 20.1)
- $10^5$–$10^6$: 12.17% (8.9, 17.5)
- $10^4$–$10^5$: 3.57% (2.7, 5.6)
- $300$–$<10^4$: 1.37% (1.0, 2.2)
- $<300$: 1.30% (1.0, ref pink)

Chen et al. JAMA 2006
HCC and HIV survival:
6 monthly AFP and ultrasound

<table>
<thead>
<tr>
<th>2 yr survival</th>
<th>HIV +</th>
<th>HIV-</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puoti (R 41)</td>
<td>11%</td>
<td>41%</td>
<td>0.01</td>
</tr>
<tr>
<td>Brau (R 63)</td>
<td>16%</td>
<td>18%</td>
<td>0.6</td>
</tr>
<tr>
<td>Berretta (R 104)</td>
<td>69%</td>
<td>72%</td>
<td>0.048</td>
</tr>
<tr>
<td>Lim (P 23-TB)</td>
<td>44%</td>
<td>60%</td>
<td>0.2</td>
</tr>
</tbody>
</table>

• All note younger age in HIV+ but other factors not common

AIDS 2004; J Hepatol 2007; oncol 2011; JAIDS 2012
HBV and HIV

• HIV increases HBV chronicity
• HBV increases antiretroviral-related hepatotoxicity
• HIV/HBV coinfection increases the risk of end stage liver disease compared to HBV alone
• HIV HBV coinfected patients have poorer hospital outcomes, more progression to cirrhosis, HCC and death than either HIV or HBV monoinfected patients

HBV-HIV Summary

• Immune response predicts HBV outcome
• Flares in HBV/HIV patients are common
  – Many HIV medications are hepatotoxic
  – Other causes of ALT elevations in HBV/HIV should be sought
  – Less common causes of flares now are ART without HBV therapy and stopping ART
• Atypical serologies may occur in HIV patients during ART
  – Reverse seroconversion occurs
• All HBV HIV patients require screening for HCC
Treatment of HBV in Pregnancy

Check HBV-DNA at week 26-28

- <20,000 IU/mL
  - No treatment

- >20,000 but <200,000 IU/mL
  - Consider treatment of mother if active HBV disease (ie, per usual treatment indications)

- >200,000 IU/mL
  - Antiviral therapy up to delivery (or one month post-partum)

Summary

- Treat if elevated ALT and HBV DNA (and special considerations)
- Comorbidities occur in patients with HBV
  - Check HIV, HCV, HDV, HAV, MS
- HBV patients should report to their primary care provider of any new diagnoses or planned therapies so that considerations for HBV antiviral therapy can be made, particularly
  - If receiving high-dose steroids, chemotherapy, or rituximab
  - If pregnant or wishing to become pregnant
- Screen for HCC with 6 monthly imaging and ALF
Strategies to Eradicate HBV

Virologic approaches

- Entry inhibitors
- Block cccDNA
- Transcription inhibitors
- RNA interference
- HBV capsid inhibitor
- Polymerase inhibitors
- Secretion inhibitors

Host immune approaches

- Interferons
- TLR-7
- PD-1/ PDL-1
- IL-7
- Therapeutic vaccines
  - Immune complex vaccines
  - Nasal HBV (NASVAC) vaccines
  - DNA vaccines
  - T cell vaccines
  - Adenovirus based vaccines (TG1050)
  - Yeast based vaccines
HBsAg subviral particles

HBeAg (P14-17)

Mature HBV virion

Mature
Nucleocapsid

ASSEMBLY AND SECRETION

Precore Protein (p25)

HBeAg

(P14-17) spherical

NUCLEAR
TRANSPORT

ENTRY

NTCP

HSPG

TRANSCRIPTION

Transcription

Precore mRNA

Pre-S1 mRNA

Pre-S2/S mRNA

Pregenomic RNA

HBx mRNA

cccDNA

DNA Repair

TRANSLATION

Precore Protein (p25)

HBsAg proteins:

LHBsAg

MHBsAg

SHBsAg

RC-DNA

see more

Mature Nucleocapsid

RT

Imature Nucleocapsid

ENCAPSIDATION

Core + pg RNA

+ Polymerase

Intracellular Conversion Pathway