Hepatitis B: An Overview & Update

Arun Jesudian, MD, FACG
Director of Inpatient Liver Services
Weill Cornell Medicine
Disclosures

• No Disclosures
Learning Objectives

By the end of this presentation, participants will be able to:

• Describe the epidemiology of hepatitis B (HBV) infection
• Understand the natural history of HBV infection
• Identify candidates for HBV vaccination
• Identify patients who should be screened for HBV and interpret HBV serology
• Educate patients on preventing HBV transmission
• Define the goals of HBV therapy and how current therapies reduce disease progression
• Follow the key steps in HBV pretreatment evaluation and treatment algorithm
• Recall the role of the primary care provider (PCP) in HBV care
Epidemiology
Global HBV Prevalence, 2016

- 292 million persons (3.5% population) infected
- 68% in Africa and Western Pacific
- 2.7 million co-infected with HIV
- Most infected persons born before HBV vaccine was widely used in infancy

Source: Lancet Gastroenterology & Hepatology 2018
HBV in the U.S.

- Up to 2.4 million infected
- 60% unaware of infection
- Only 50,000 HBV prescriptions a year

Figure from Cohen et al. Journal of Viral Hepatitis 2011: 18, 377-383
Gaps in HBV Care in the U.S.

- Up to 40% of HBV-infected persons develop cirrhosis, HCC, or liver failure
  - 25% die prematurely
  - Indirect/direct health care costs: $1 billion
- Vaccination and screening can reduce this burden
  - Only 25% of U.S. adults have been completely vaccinated
  - 60% of infected persons are unaware of their infection
  - Only 10-15% of eligible patients have been treated

95,617 people are reported with Hepatitis B in NYC from 2016-2019 (2019 Annual Report)
95,617 people are reported with Hepatitis B in NYC from 2016-2019 (2019 Annual Report)

Only 54% are aware of their status (Moore, et al., Public Health Rep, 2019)
Hepatitis B - Facts

95,617 people are reported with Hepatitis B in NYC from 2016-2019
(2019 Annual Report)

Only 54% are aware of their status
(Moore, et al., Public Health Rep, 2019)

Without treatment and monitoring
15-25% of people will die prematurely from cirrhosis, liver failure, or liver cancer
(Cohen, et al., Journal of Community Health, 2013)
Foreign-born persons comprise 14% of the U.S. population but 60-90% of people living with chronic HBV.

Top countries of origin of foreign-born persons with HBV (by number of people):
1. China
2. Vietnam
3. Philippines
4. India
5. Dominican Republic
6. Taiwan

HBV prevalence rate among foreign-born persons by region of birth (2012):
- **Africa** (8.7%)
  - Liberia (16.5%)
  - Guinea (14.9%)
- **Asia** (5.9%)
  - Taiwan (13.0%)
  - Vietnam (11.7%)
- **Oceania** (4.5%)
  - Micronesia (14.28%)
  - Tonga (12.0%)

HBV Infection in Foreign-Born Population, National

Viral Hepatitis is Underfunded

- Those affected are the silent minorities, no political voice
- Health disparity/equity issue
  - We have the tools – vaccine, medications for cure/treatment, medical knowledge
  - Those most at-risk are falling through the system


<table>
<thead>
<tr>
<th>Virus</th>
<th>US population</th>
<th>% of CDC division budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>0.8-2.2 million</td>
<td>2% (for both HBV/HCV domestic/international)</td>
</tr>
<tr>
<td>HCV</td>
<td>2.7-3.9 million</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>1.1 million</td>
<td>69% (domestic, not including international HIV work)</td>
</tr>
</tbody>
</table>
Natural History
HBV Structure

- DNA virus
- Ten genotypes, A to J
- HBV replicates through an RNA intermediate and can integrate into the host genome
- Virological and serological assays have been developed for diagnosis of various forms of HBV-associated disease
<table>
<thead>
<tr>
<th></th>
<th>Immune-Tolerant CHB</th>
<th>Immune-Active CHB</th>
<th>Inactive CHB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBV test results</strong></td>
<td>HBsAg present for 6 months</td>
<td>HBsAg present for 6 months</td>
<td>HBsAg present for 6 months</td>
</tr>
<tr>
<td></td>
<td>HBeAg positive</td>
<td>Serum HBV DNA &gt;20,000 IU/mL in HBeAg-positive CHB</td>
<td>HBeAg negative, anti-HBe positive</td>
</tr>
<tr>
<td></td>
<td>HBV-DNA levels are very high (typically &gt;1 million IU/mL)</td>
<td>&gt;2,000 IU/mL in HBeAg-negative CHB</td>
<td>Serum HBV DNA &lt;2,000 IU/mL</td>
</tr>
<tr>
<td><strong>ALT/AST levels</strong></td>
<td>Normal or minimally elevated</td>
<td>Intermittently or persistently elevated</td>
<td>Persistently normal</td>
</tr>
<tr>
<td><strong>Liver biopsy or noninvasive test results</strong></td>
<td>no fibrosis and minimal inflammation</td>
<td>chronic hepatitis with moderate or severe necroinflammation and with or without fibrosis</td>
<td>absence of significant necroinflammation (biopsy); variable levels of fibrosis</td>
</tr>
</tbody>
</table>
Disease Burden from HBV Infection: 5-Year Cumulative Incidence Rates of Development of Chronic HBV Complications


Acute Infection → Chronic Infection

Chronic Infection → Cirrhosis

8%-38%¹

0.1%-3%¹

Liver Failure ( Decompensation) → Cirrhosis

15%¹

Liver Transplantation

Liver Failure ( Decompensation) → HCC

10%-17%¹

HCC → Death

70%-85%¹

Death
REVEAL Study: All-Cause and Liver-Related Mortality in Patients with HBV

**Total mortality according to HBsAg status (n=22,472)**

- **HBsAg+**
- **HBsAg-**

Survival vs Year of Follow-Up

- Survival decreases over time for both groups.
- **HBsAg+** has lower survival compared to **HBsAg-**.
- Statistical significance: \( P < 0.001 \)

**Liver-related mortality by baseline HBV DNA in HBsAg+ subjects without evidence of HCV infection (n=3,653)**

- Baseline HBV DNA Level:
  - ≥1 million
  - 100,000 - 999,999
  - 10,000 - 99,999
  - 300 - 9,999
  - <300

Survival vs Year of Follow-Up

- Different survival rates based on DNA level.
- Statistical significance: \( P < 0.001 \)

REVEAL Study: Progression to HCC and Liver-Related Death in HBeAg Negative Chronic Infection


Cumulative hazard of progression to HCC

Cumulative hazard of progression to liver-related death

Cumulative hazard of progression to HCC

- Control
- HBeAg Negative Chronic Infection (HBV DNA <10,000 copies/mL and ALT <45 U/L)

Cumulative hazard of liver-related death

- $P < .001$ by log-rank test

- $P = .029$ by log-rank test
Prevention
HBV Vaccination: Infants and Children

- Infants:
  - First dose of HBV vaccine at birth
  - Complete the series at 6 months of age

- Unvaccinated children <19 years
HBV Vaccination: At Risk Adults

- Adults at risk by **sexual exposure**
  - sex partners of HBsAg+ persons
  - persons with multiple sex partners
  - persons seeking STI treatment
  - men who have sex with men
- Adults at risk by **percutaneous or mucosal exposure**
  - injection drug users
  - household contacts of HBsAg+ persons
  - incarcerated, health care and public safety workers
- Adults with chronic liver disease, end-stage renal disease (incl. hemodialysis patients), or HIV infection
- Pregnant women at risk for infection
- Travelers to HBV endemic regions
- Adults seeking protection from HBV infection

Gaps in HBV Vaccination

- Adult HBV vaccine coverage is low.
- Only 31% of primary care physicians reported routinely assessing for and vaccinating adults with HBV risk factors.
- Similarly, among men who have sex with men (MSM) surveyed in the Young Men's Health Study, only 17% had received hepatitis B vaccine.

Source: HBV Immunizations. Hepatitis B Online. https://www.hepatitisb.uw.edu/go/prevention-hbv/hbv-immunizations/core-concept/all#background

*https://www.cdc.gov/vaccines/acip/*
Preventing HBV Transmission: Educating Patients

Tell patients:

• Use condoms during sex until partners is fully vaccinated against Hep B.
• Use only new or sterile equipment for injection (e.g. drugs, insulin, steroids), tattooing, or acupuncture
• Ensure household and sexual contacts are tested and vaccinated
• Avoid sharing toothbrushes, razors, needles, nail clippers, nail scissors or washcloths
• Cover cuts and sores, wash hands after touching your blood or body fluids
• Clean blood spills with bleach solution
• Do not donate blood, organs or sperm

HBV-infected children and adults:

• **Can** participate in all activities including contact sports
• **Should not** be excluded from daycare or school participation and should not be isolated from other children
• **Can** share food, utensils, or kiss others

Source: NYC Health Department
Screening & Diagnosis
HBV Tests Part I: All Patients Need this “Triple Panel” When Evaluating for HBV

- +HBsAg = infection (Test all patients for HDV)
- +Anti-HBc = exposure = cccDNA = persistence
  - Eval for Occult HBV if HBsAg (-)
  - Reactivation risk
  - No vaccine boosting
- +Anti-HBs = immunity, if anti-HBc is negative

Note:
- HBV is incurable
- There is no “natural immunity”
# Interpreting HBV Test Results

<table>
<thead>
<tr>
<th>Clinical state</th>
<th>HBsAg</th>
<th>anti-HBs</th>
<th>anti-HBc</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic infection</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Evaluate for treatment</td>
</tr>
<tr>
<td>Acute infection</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Link to HBV directed care</td>
</tr>
<tr>
<td>(IgM anti-HBc)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolved infection</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Counseling, reassurance</td>
</tr>
<tr>
<td>Immune (immunization)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Reassurance</td>
</tr>
<tr>
<td>Susceptible (never infected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Vaccinate</td>
</tr>
<tr>
<td>or immunized)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposed</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Depends on situation</td>
</tr>
</tbody>
</table>

www.cdc.gov/hepatitis
Other Recommended Testing With HBV Diagnosis

- **Test for coinfection:**
  - Hepatitis Delta virus (HDV) in HbsAg-positive persons
    - Especially HbsAg positive patient with low HBV DNA and high ALT
    - Consider treatment with Peg-IFN-a for 12 months
  - HIV
    - Initiation of ART
  - Hepatitis C virus (HCV)
    - Treat HCV with antiviral therapy once on HBV treatment
High-Risk Groups for HBV Screening

- Persons requiring immunosuppressive therapy
- Persons with end-stage renal disease (including hemodialysis patients)
- HCV infected persons
- Persons with elevated ALT (≥19 IU/L for women and ≥30 IU/L for men)
- Persons who have been incarcerated
- Pregnant women*
- Infants born to HBV infected people

*The 1990 NYS Public Health Law Article 25, Section 2500-e (Appendix A) mandates HBsAg testing of all pregnant women.

Important risk groups for HBV infection with a prevalence of ≥2% that should be screened include:

- Persons born in countries and regions with a high prevalence of HBV infection (≥2%), such as Asia, Africa, the Pacific Islands, and parts of South America
- US-born persons not vaccinated as infants whose parents were born in regions with a very high prevalence of HBV infection (≥8%)
- HIV-positive persons
- Persons with injection drug use
- Men who have sex with men
- Household contacts or sexual partners of persons with HBV infection
Underscreening of HBV

- Even among Asian-American PCPs with a large percentage of Asian patients, only 50% routinely screen their Asian patients for HBV
- Stated reasons for not ordering a screening test in Asian patients included:
  - Patients not considered to be at risk for HBV (23%)
  - No symptoms (16%)
  - Patient has received vaccination series (15%)
  - Lack of insurance (13%)

Treatment
HBV Therapy Reduces Risk of Disease Progression

Prospective cohort study in HBV pts with first-onset complications of decompensated cirrhosis (n = 707) treated predominantly with lamivudine (n = 203) or entecavir (n = 19)

Antiviral therapy improved transplant-free survival over mean follow-up of 49 mos ($p = .0098$ vs untreated)

*Nonresponders included pts with HBV rebound or genotypic resistance, primary nonresponse, Not evaluable due to early event (death, LT, LTFU).
Prospective cohort study in pts with HBV and first-onset complications of decompensated cirrhosis (n = 707)


Antiviral therapy improved transplant-free survival over 5 years (p = .0098 vs untreated)

Bonferroni-adjusted P < .0003
Pretreatment Evaluation: History and Physical Examination

- Risk factors for viral hepatitis
- Duration of infection
- Route of transmission
- Risk factors for HIV co-infection
- Alcohol history
- Presence of comorbid diseases

- Family history of liver cancer
- HBV testing of family members
- General counseling regarding transmission
- Vaccination of at-risk household and sexual contacts
- Family planning

Goals of HBV Therapy

- Improve liver histology
- Decrease serum HBV DNA levels
- Seroconversion (loss of HBeAg, development of anti-HBe, loss of HBsAg, development of anti-HBs)
- ALT normalization

• Prevention of death, cirrhosis, and HCC
• Reduce infectivity and stigma
What About a Cure?

Types of HBV Cure

• Inactive state
  – Sustained, off drug
    • No inflammation – Normal ALT and liver biopsy
    • HBVDNA low or undetectable
    • HBsAg positive

• Functional Cure (Clinical Resolution)
  – Sustained, off drug
    • No inflammation – Normal ALT and liver biopsy
    • HBsAg loss
    • Anti-HBs gain

• Complete Cure (Virologic Cure)
  – All of the above plus
  – Loss of cccDNA in the liver
FDA Approved Therapies

- **First line therapy**
  - 2005: Peg interferon alfa-2a (PEGASYS®), Roche
  - 2005: Entecavir (BARACLUDE™), Bristol-Myers Squibb
  - 2008: Tenofovir disoproxil fumarate (VIREAD®), Gilead
  - 2016: Tenofovir alafenamide (VEMLIDY®), Gilead

- **Second line therapy**
  - 2002: Adefovir dipivoxil (HEPSERA™), Gilead
  - 2006: Telbivudine (TYZEKA™), Idenix and Novartis

- **Third line therapy**
  - 1998: Lamivudine (EPIVIR-HBV®), GlaxoSmithKline

Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
American Association for the Study of Liver Diseases
Algorithm for Treatment Decisions in HBV

Elevated ALT > 2X ULN
- HBeAg positive
  - HBV DNA > 20,000 IU/ml
- HBeAg negative
  - HBV DNA > 2000 IU/ml

Elevated ALT < 2X ULN
- HBeAg positive
  - HBV DNA > 20,000 IU/ml
- HBeAg negative
  - HBV DNA > 2000 IU/ml

Continue to monitor ALT
Consider Fibroscan and/or liver biopsy if > 40 yrs and/or ALT > ULN
If significant fibrosis or inflammation

AASLD HBV Treatment Recommendations

- Patients with cirrhosis, regardless of e antigen status or ALT level with detectable HBV DNA should be treated.
- Patients with normal ALT and HBV DNA > 1,000,000 IU/ml, regardless of E antigen status, should be treated if there is moderate to severe inflammation/fibrosis and/or > 40 years of age.

<table>
<thead>
<tr>
<th>Name</th>
<th>Anti-viral Potency</th>
<th>Side effects</th>
<th>Risk of resistance</th>
<th>Caveats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN alfa 2a</td>
<td>++</td>
<td>Fatigue, cytopenias, depression</td>
<td>None</td>
<td>Not recommended in cirrhosis, cardiopulmonary disease, psychiatric disease, uncontrolled seizures, pregnancy</td>
</tr>
<tr>
<td>Entecavir</td>
<td>+++</td>
<td>Lactic acidosis</td>
<td>Very low</td>
<td>Not recommended if prior nucleoside analogue treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dose adjustment if Cr cl &lt; 50 ml/min</td>
</tr>
<tr>
<td>TDF</td>
<td>+++</td>
<td>Renal and bone toxicity</td>
<td>Very low</td>
<td>Dose adjustment if Cr cl &lt; 50 ml/min</td>
</tr>
<tr>
<td>TAF</td>
<td>+++</td>
<td>Minimal renal and bone toxicity</td>
<td>Very low</td>
<td>Dose adjustment if Cr cl &lt; 15 ml/min</td>
</tr>
</tbody>
</table>
Reversal of Fibrosis and Cirrhosis: Tenofovir Phase III Trial: Biopsies at Year 0, 1 & 5

- 348 / 641 (54%) had liver biopsy at baseline and Year 5
- 71 / 96 (74%) with cirrhosis (Ishak Score ≥5) at baseline no longer had cirrhosis at Year 5
Sample Case

- 36 year old Asian women
- History of hepatitis B with risk factor pre-natal transmission
- Feels well
- ALT 55
- HBVDNA 120,000 IU
- Platelet count 185,000
- HBsAg +
- HBeAg+
- F1 on transient elastography

What do you do now?
- Screen for HCC q 6 months
- Initiate HBV anti-viral therapy
Sample Case

- 39 year old Asian man
- History of hepatitis B with risk factor pre-natal transmission
- Feels well
- ALT 30
- HBVDNA 1200 IU
- Platelet count 285,000
- HBsAg +
- HBeAg-
- F1 on transient elastography

What do you do now?
- Screen for HCC q 6months
- Do not start HBV anti-viral therapy
  - Follow with ALT, HBVDNA every 3-6 months
HBV and Pregnancy
Suggested Management of HBV Infection During Pregnancy

HBsAg+

Yes

HBV DNA >10^6 copies/mL (200,000 IU/ml)

Refer for consideration for treatment with TDF at Week 28

Infant receives HBIG + HBV vaccine at birth

HBV DNA <10^6 copies/mL

*May consider treatment if previous child HBV+.

Role of PCP in HBV Care

- Link HBV infected patients to treatment centers
- Follow patients on therapy every 3-6 months with:
  - Liver enzymes
  - HBV DNA
- HCC surveillance every 6 months with U/S and AFP regardless of whether patient is on treatment or not
- Discuss modes of transmission and prevention
- Discuss HBV testing and vaccination for close contacts
- Vaccinate for hepatitis A if susceptible
- Screen for HCV