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
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
• 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)
Hepatitis B - Facts

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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)
HBV Infection in Foreign-Born Population, National

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

<table>
<thead>
<tr>
<th>Virus</th>
<th>US population</th>
<th>% of CDC division budget</th>
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</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>
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</tr>
<tr>
<td>HIV</td>
<td>1.1 million</td>
<td>69% (domestic, not including international HIV work)</td>
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- 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

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

Source: basicmedicalkey.com

Liang JT, Hepatology. 2009 May ; 49(5 Suppl): S13–S21
### AASLD Guidelines: Diagnostic Criteria and Definitions for Chronic HBV

<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**
  - 8%-38%\(^1\) → **Cirrhosis** → **Liver Failure ( Decompensation)** → **Liver Transplantation** → **Death**
  - 0.1%-3%\(^1\) → **HCC** → **Liver Transplantation**
  - 70%-85%\(^1\) → **Liver Transplantation**
  - 15%\(^1\) → **Liver Transplantation**
  - 10%-17%\(^1\) → **Liver Transplantation**
REVEAL Study: All-Cause and Liver-Related Mortality in Patients with HBV

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

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

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


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 progression to liver-related death

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

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.
- *11/2021: An updated recommendation from the Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) calls for universal hepatitis B vaccination of all adults aged 59 and younger

*https://www.cdc.gov/vaccines/acip/

Source: HBV Immunizations. Hepatitis B Online. https://www.hepatitisb.uw.edu/go/prevention-hbv/hbv-immunizations/core-concept/all#background
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></td>
<td></td>
<td></td>
<td>(IgM anti-HBc)</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 or immunized)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Vaccinate</td>
</tr>
<tr>
<td>Exposed</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Depends on situation</td>
</tr>
</tbody>
</table>

[www.cdc.gov/hepatitis](http://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 $P < .0003$

- Treated,* responder (n = 245)
- Treated,* nonresponder (n = 178)
- Untreated (n = 284)

*Treated predominantly with lamivudine (n = 203) or entecavir (n = 198).

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.

# Anti-Viral Treatment Options for HBV

<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 6months
- 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 6 months
- 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
    - **HBV DNA <10^6 copies/mL**
      - Infant receives HBIG + HBV vaccine at birth

*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