Clinical Management of Hepatitis B

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Disclosures

• No Disclosures
The Empire Liver Foundation is an association of NYS liver specialists dedicated to increasing community awareness of liver disease, providing education on liver disease to health care providers and patients and providing guidance to those who make policy decisions influencing the practice and science of liver disease.

- CME Grand Rounds
- CME Clinical Training Series
- Live Preceptorship
- Mentoring

www.empireliverfoundation.org

The New York City Health Department Viral Hepatitis Program conducts surveillance and develops and implements programs to build capacity to prevent, manage and treat hepatitis B and C in New York City.

- Surveillance
- Community Coalitions
- Navigation Programs
- Clinical Practice Facilitation
- Training

www.HepFree.NYC
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)
Hepatitis B - Facts

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

In 2019:
- 5,964 newly reported chronic HBV cases
- Neighborhoods with highest rates were:
  - Sunset Park East, Brooklyn
  - Flushing, Queens
- More than half of residents of both neighborhoods are foreign-born (largely from China, Korea and Mexico)

Source: NYC Health Department, 2020
HBV-Infected Pregnant Women in NYC: Region of Birth

Percentage of people with hepatitis B who delivered a live birth in New York City by region of birth, 2019

- China: 52.9%
- Western Africa: 17%
- Caribbean and Haiti: 5.3%
- West and Central Asia: 4.9%
- Europe: 4.2%
- South Asia: 4%
- U.S.: 3.2%
- East Asia (excluding China): 2.6%
- Southeast Asia: 2.5%
- Mexico, Central and South America: 1.7%

Source: NYC Health Department, 2019
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
# 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>

- CHB: Chronic Hepatitis B
- HBsAg: Hepatitis B surface antigen
- HBeAg: Hepatitis B e antigen
- ALT: Alanine aminotransferase
- AST: Aspartate aminotransferase
- IU/mL: International Units per milliliter
Disease Burden from HBV Infection:
5-Year Cumulative Incidence Rates of
Development of Chronic HBV Complications

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

$P < .001$ by log-rank test

Control

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

Cumulative hazard of progression to liver-related death

$P = .029$ by log-rank test

Prevention
HBV Vaccination: Infants, Children, Adults

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

• Unvaccinated children <19 years

• CDC recommends HBV vaccination for all adults 19-59
  – 11/3/2021
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

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</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Vaccinate</td>
</tr>
<tr>
<td>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
    - New therapies for HDV are being developed
  - HIV
    - Initiation of ART
  - Hepatitis C virus (HCV)
    - Check for HBV prior to starting HCV antiviral therapy
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
TREAT
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 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
  - **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

New York State
HBV Clinical Capacity
Building Resources
HBV Training Opportunities & Resources in NYS

There are many HBV training opportunities and resources, most offering CMEs:
• CME training (live/webinar) on HBV care and treatment
• HBV evaluation and linkage to care guidance and technical assistance
• HBV clinical preceptorships

www.hepfree.nyc

To learn more contact: Hep@health.nyc.gov

Or contact the NYC Health Department Warm line: 917-890-0834
Additional Clinical Resources

• National Task Force on Hepatitis B: [www.hepbtaskforce.org](http://www.hepbtaskforce.org)

• University of Washington Hepatitis B Online: [https://www.hepatitisb.uw.edu](https://www.hepatitisb.uw.edu)

HBV Care Resources in NYC

- **Check Hep B Patient Navigation Program**
  - Provides free or low cost Hep B Patient Navigation services at eight organizations in NYC. Patient Navigators assist patients with complete testing, linkage to care, support through a full medical evaluation and treatment if recommended. [https://hepfree.nyc/check-hep-b-patient-navigation-program/](https://hepfree.nyc/check-hep-b-patient-navigation-program/)

- **Linkage to Care Affordable Care Support**
  - Health Department HBV testing and care services listing
    - [www.nyc.gov/health/hepb](http://www.nyc.gov/health/hepb)
    - NYC Health Department Health Map
  - Health Care Access Specialist
    - 917-890-0834
    - [Hep@health.nyc.gov](mailto:Hep@health.nyc.gov)
HBV Care Resources in NYC

• Patient Assistance Programs
  – cover the cost of medication and copays for uninsured
• Order HBV Patient Education Materials: Hep@health.nyc.gov
• NYC Hep B Coalition: www.HepFree.NYC
Additional Clinical Guidance

Prevention:
• HBV vaccines: https://www.hepatitisb.uw.edu/page/treatment/vaccines
• Perinatal HBV prevention: https://www1.nyc.gov/site/doh/providers/health-topics/hepatitis-b-and-pregnancy.page

Screening:
• USPSTF screening guidelines: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-b-virus-infection-screening
• HBV Primary Care Workgroup recommendations: https://www.hepatitisb.uw.edu/page/primary-care-workgroup/guidance
• HBV screening tests: https://www.hepatitisb.uw.edu/go/screening-diagnosis/diagnosis-hbv/core-concept/all#recommended-screening-tests

Patient education:
• Order HBV patient education materials: Hep@health.nyc.gov
For CMEs or educational opportunities, contact:

Meg Chappell, MPH
Program Manager
Empire Liver Foundation
megchappell@empireliverfoundation.org
www.empireliverfoundation.org

For questions about resources, contact:

Marie P. Bresnahan, MPH
Director, Training, Policy, and Administration
Viral Hepatitis Program
Bureau of Communicable Disease
mbresnahan@health.nyc.gov
www.hepfree.nyc
# Hepatitis B Training Series

<table>
<thead>
<tr>
<th>Date &amp; Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>January 13, 2022 @ 4:30PM</td>
<td>Hepatitis B: Epidemiology, Screening and Prevention with Paul Gaglio, MD</td>
</tr>
<tr>
<td>January 20, 2022 @ 4:30PM</td>
<td>Hepatitis B Pre-Treatment Evaluation and Treatment Initiation with Lisa Ganjhu, DO</td>
</tr>
<tr>
<td>January 27, 2022 @ 4:30PM</td>
<td>Management of Hepatitis B and Treatment Monitoring with Harmi Kalia, DO</td>
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