Hepatitis B
Epidemiology and Natural History and Implications for Treatment

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Disclosures
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Consultant: Dynavax, Novartis
Prevalence of Chronic Hepatitis B

Estimated 248 million HBsAg positive globally (2010)

Schweitzer A, Lancet 2015;386:1546-55
Estimating HBV Disease Burden in Foreign-born Americans

Country-specific pooled CHB prevalence rates multiplied by # of FB living in U.S. in 2009 by country of birth to yield total # of FB with CHB in U.S.

3.4% of FB in U.S. have chronic hepatitis B

Total with CHB may be as high as 2.2 million

Chronic HBV Cases in U.S.

Majority among Foreign Born

Reflected in CDC Guidelines for HBV Screening

- Persons born in countries with ≥ 2% HBsAg prevalence
- US-born persons not vaccinated as infants whose parents were born in regions with ≥ 8% HBsAg prevalence

CDC Estimates

# Prevalence of HDV Infection in the US

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>% of HBsAg+ Population Tested for anti-HDV</th>
<th>Prevalence of Anti-HDV Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>25,603</td>
<td>8.5%</td>
<td>3.4%</td>
</tr>
<tr>
<td>California liver practice</td>
<td>1,191</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>HBRN (U.S. &amp; Toronto)</td>
<td>1,507 Adult 181 Peds</td>
<td>100%</td>
<td>3.2% 1.1%</td>
</tr>
</tbody>
</table>

Anti-HDV prevalence highest FB from Africa and East Mediterranean regions

Total with HDV may be as high as 77,000

Routes of Transmission Vary Depending on Prevalence of Infection in the Population

More common among foreign-born:
- Perinatal
- Horizontal

More common among American-born:
- Transplantation
- Occupational
- Nosocomial
- IDU
- Sexual
Risk of Chronic HBV After Acute HBV Varies with Age of Exposure

- **Acute Infection**
  - **Subclinical Hepatitis**: 5-20%
  - **Clinical Acute Hepatitis**: 80-95%
  - **Fulminant Hepatitis**: <1%
  - **Death**: 0.1-2.7%
  - **Recover**:
  - **Chronic Infection**:
    - Risk of Chronic Infection:
      - Neonate: 90%
      - Children: 20%
      - Adults: <5%
Acute to Chronic Infection with Phases

- Early Childhood: >95% Immune Tolerance
- Adult hood: <5% Immune Tolerance
- HBeAg- Chronic Hepatitis B
- Cirrhosis
- HCC
- HBeAg+ Chronic Hepatitis B
- Inactive Carrier
- Immunity HBsAg Clearance
5-Year Complication Rate in Chronic HBV Infection

- Chronic Hepatitis B
  - Cirrhosis: 12-20%
  - Decompensated Cirrhosis: 20-23%
  - Liver Cancer: 10-25%

Fattovich, Hepatology, 1995; Fattovich, Gut, 1991
Liaw, Hepatology, 1988; Liaw, Liver, 1989
## Annual Age-Adjusted Death Rate Due to Chronic HBV

Mortality data from 1999 to 2007 from the National Center for Health Statistics

<table>
<thead>
<tr>
<th>Underlying/contributing cause of</th>
<th>Total Deaths</th>
<th>Age-adjusted 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>15,106</td>
<td>4.58 (4.50-4.67)</td>
</tr>
<tr>
<td>HIV</td>
<td>12,734</td>
<td>4.16 (4.09-4.24)</td>
</tr>
<tr>
<td>HBV</td>
<td>1,815</td>
<td>0.56 (0.54-0.59)</td>
</tr>
</tbody>
</table>

*Ly C, Ann Intern Med 2012;156:271-8*
## Characteristics of Decedents with HBV Listed as Cause of Death

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (unadjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2.9</td>
</tr>
<tr>
<td>Age (ref: &lt;45)</td>
<td></td>
</tr>
<tr>
<td>45-54 yrs</td>
<td>2.3</td>
</tr>
<tr>
<td>55-64 yrs</td>
<td>1.5</td>
</tr>
<tr>
<td>≥65 yrs</td>
<td>0.2</td>
</tr>
<tr>
<td>Race (ref: white)</td>
<td></td>
</tr>
<tr>
<td>Black, NH</td>
<td>2.6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.4</td>
</tr>
<tr>
<td>Asian/Pac Isl.</td>
<td>17.5</td>
</tr>
<tr>
<td>Am/Alaskan Native</td>
<td>1.3</td>
</tr>
<tr>
<td>HIV</td>
<td>11.1</td>
</tr>
<tr>
<td>Alcohol</td>
<td>8.1</td>
</tr>
<tr>
<td>Coinfection HCV</td>
<td>70.3</td>
</tr>
</tbody>
</table>

*Ly C, Ann Intern Med 2012;156:271-8*
HBV: Epidemiology

- Estimated 2.2 million with chronic HBV infection
- Chronic infections largely among foreign-born (FB)
  - Most are Asians and Africans who are typically infected as infants and children
  - American-born infections typically acquired as adolescents and adults
- Risk of liver-related complications highest if cirrhosis
- Deaths due to HBV are declining, likely reflecting benefits of antiviral therapy
  - Comorbidities important: alcohol, HCV, HDV
Natural History of Chronic HBV Infection

- Dynamic disease
  - Life-long monitoring
  - Treatment is selective

- Not curable
  - HBV can be suppressed but not eliminated
  - Barriers to cure:
    - Integration into host DNA
    - cccDNA reservoir (not affected by nucleoside analogues)
HBV Cure: How is it Defined?

- **True Cure** of infection
  - True cure = all traces of HBV gone from the liver (ie. like HCV)
  - This is VERY difficult (if not impossible) → cccDNA

- **Functional cure**
  - HBsAg loss (ideally with anti-HBs)
  - Infrequently achieved

- More frequently achieved and associated with low risk of future complications: *Sustained off treatment inactive disease*
  
  = HBeAg –ve, HBV DNA undetectable, normal ALT but HBsAg positive
Phases of Chronic HBV

<table>
<thead>
<tr>
<th>Phase</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Immune tolerant
- Immune clearance HBeAg +ve CHB
- Inactive CHB
- Reactivation HBeAg –ve CHB
- HBsAg cleared

Highlights need for regular monitoring and reassessment of phase – need to intervention.
25-Yr Survival Rates in Untreated Chronic HBV

Survival probability (%)

Time (years)

HBsAg+, HBeAg –ve, HBV DNA undetectable

HBeAg-/HBV DNA+ or HBeAg reversion

HBeAg+ persistence

Fattovich et al. Gut 2008
Risk of HCC Among Patients with Chronic HBV

- REVEAL: long-term follow-up (mean, 11.4 yrs) of untreated HBsAg positive individuals in Taiwan (N = 3653)

HBV DNA Level and All-Cause Mortality

Threshold of HBV DNA ≥20,000 IU/mL (=100,000 copies/ml) is criterion used to define who should be treated

Viral load presented as copies/mL.

Phases of Chronic HBV
Active Disease Warrants Treatment

Phase 1: Immune tolerant
- HBeAg positive
- HBV DNA >20,000 IU/mL
- ALT ≥2 ULN

Phase 2: Immune clearance HBeAg +ve CHB
- HBeAg positive
- HBV DNA >20,000 IU/mL
- ALT ≥2 ULN

Phase 3: Inactive CHB
- HBeAg negative (precore/BCP mutation)
- HBV DNA >2000 IU/mL
- ALT ≥2 ULN

Phase 4: Reactivation HBeAg -ve CHB
- HBeAg negative (precore/BCP mutation)
- HBV DNA >2000 IU/mL
- ALT ≥2 ULN

Phase 5: HBsAg cleared
Summary

HBV: Natural History

- Dynamic disease with variable HBV DNA and ALT levels over time
  - Life-long monitoring (minimum every 6 months)
- HBV DNA predicts risk of liver-related complications
  - Threshold for risk ~2000-20,000 IU/mL
- Advanced fibrosis also important; risk significantly higher if cirrhosis
- Goal of current therapy is to achieve sustained virologic control (HBV DNA undetectable) on or off treatment
- Patients in immunologically active phases are target groups for therapy
Chronic HBV: Life-Long Management

- Balancing benefit and risk in the absence of curative therapy

- **TREAT NOW**
  - Significant or severe liver disease

- **TREAT NOW OR MONITOR?**
  - Predicting future risk

- **MONITOR**
  - Defer Treatment Until Clear Indication

Risk of Cirrhosis, Liver Failure and Liver Cancer

Adapted from A Lok
Treatment of Immune Active CHB: Who and With What?

<table>
<thead>
<tr>
<th>Criteria for Antiviral Therapy</th>
<th>Insufficient data to support or refute treatment with ALT &gt;ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) ALT &gt; 2 X ULN (M&gt;60, F &gt;38)</td>
<td>&gt;20,000 IU/mL if HBeAg+</td>
</tr>
<tr>
<td>2) Sufficient HBV DNA</td>
<td>&gt;2000 IU/mL if HBeAg neg</td>
</tr>
<tr>
<td>HBV DNA compatible with IA</td>
<td>Family history of HCC</td>
</tr>
<tr>
<td>disease</td>
<td>Older age (&gt;40)</td>
</tr>
<tr>
<td>3) Other factors to consider</td>
<td>Presence of cirrhosis</td>
</tr>
</tbody>
</table>

Preferred Treatments

- Peginterferon alfa-2a
- Entecavir (ETV)
- Tenofovir dipoxovil fumarate (TDF)
- [Tenofovir Alafenamide (TAF)]

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault N, Hepatology 2016;63;261-83
“Indeterminant” Phenotypes are Frequent

HBRN study: based on enrollment into longitudinal cohort
HBeAg-negative patients: % with elevated ALT and HBV DNA (>104 IU/mL)
Normal ALT >30U/L for males, >20 U/L for females

38% of patients do not fit into the defined categories

Dibisceglie A, J Viral Hepat 2017 Apr;24(4):320-329
Algorithm Used to Determine Need for Treatment

**HBeAg Positive**
- HBV DNA >20,000 IU/mL

**HBeAg Negative**
- HBV DNA >2,000 IU/mL

**ALT Evaluation**

**Elevated ALT (≥2 ULN)**
- Treat

**Normal ALT**
- Monitor ALT
- Consider Liver Biopsy If >40 yrs
- Significant fibrosis or inflammation

AASLD Treatment Guidelines 2016
The natural history of chronic HBV with and without antiviral therapy influences the AASLD treatment recommendations

A few examples......
Approach to Management of Adults with Immune-Tolerant CHB (Phase 1)

Recommendations

2A. The AASLD recommends against antiviral therapy for adults with immune-tolerant CHB.

   Quality/Certainly of Evidence: Moderate
   Strength of Recommendation: Strong

Technical Remark

1. Immune-tolerant status should be defined by ALT levels utilizing ≤30 U/L for men and ≤19 U/L for women as ULNs rather than local laboratory ULNs.

2B. The AASLD suggests that ALT levels be tested at least every 6 months for adults with immune-tolerant CHB to monitor for potential transition to immune-active or -inactive CHB.

   Quality/Certainly of Evidence: Very low
   Strength of Recommendation: Conditional

- Suggests antiviral therapy in select group:
  - Normal ALT
  - HBV DNA ≥1 million IU/mL
  - >40 years of age
  - Liver biopsy (or non-invasive test) showing significant necroinflammation or fibrosis

   Quality/Certainly of Evidence: Very low
   Strength of Recommendation: Conditional

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault N, Hepatology 2016;63;261-83
Disease Progression Minimal During Immune-Tolerant Phase

- 57 patients with high HBV DNA levels in immune-tolerant phase
  - 48 remained in immune tolerant phase at 5-year follow-up

Algorithm for Management of Patients With Cirrhosis

Compensated

- HBV DNA ≥ 2000 IU/mL
- HBV DNA < 2000 IU/mL but detectable

Recommendations

7A. The AASLD suggests that adults with compensated cirrhosis and low levels of viremia (< 2,000 IU/mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level.

Quality/Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

Decompensated

- Any HBV DNA Level
- Treat Indefinitely
- Refer for Liver Transplantation

AASLD HBV Treatment Guidelines 2016
Patients with Cirrhosis and Low Level HBV DNA: Are They at Risk?

Retrospective cohort 385 treatment-naïve, HBV-related compensated cirrhosis patients with low HBV-DNA levels (<2,000 IU/mL) followed for median of 5.6 yrs

Antiviral therapy (p=0.04) and longer duration AVT (p=0.02) associated with reduced HCC risk

Low HBV DNA but elevated ALT

Low HBV DNA but normal ALT

Undetectable HBV DNA and normal ALT

Sinn DH, Hepatology 2015;62:694-701
When to Stop Treatment

**HBeAg-positive CHB**

Stop after 

**HBeAg seroconversion with persistently normal ALT and undetectable HBV DNA for at least 12 months**

**OR**

Continue until **HBsAg seroconversion**

**Factors to consider regarding stop versus continue:**

- **Factors to consider if stop vs continue decision:**
  - Consequences of virologic relapse
  - Burden of continued treatment (adherence, cost, monitoring)
  - Patient & provider preference

- If stop therapy, necessitates close monitoring of HBV DNA and ALT every 3 mos for at least a year

- **Not recommended if cirrhosis**

*AASLD Guidelines for Treatment of Chronic Hepatitis B*  
Terrault N, *Hepatology* 2016;63;261-83
HBeAg Seroconversion is a “Seminal Event” in Natural History of CHB

- HBeAg $\rightarrow$ anti-HBe signals an improved level of immune control

- Associated with:
  - Decline in HBV DNA to low (<2000 U/ml) or undetectable levels
  - Reduced inflammation/injury in the liver
  - Decreased risk of cirrhosis, HCC and liver-related death

- HBeAg seroconversion is prerequisite for HBsAg loss $\rightarrow$ ultimate goal of therapy

- Reactivation can occur in up to 1/3 of patients
Age at HBeAg Seroconversion and Duration of Durability of Consolidation are Key

Pan X, PLOS one 2013;8:e68568

Song J, W J Gastroenterology 2012;18:6277-83
When to Stop Treatment

HBeAg-negative CHB

Continue until HBsAg seroconversion

Factors to consider regarding stop versus continue:

- Factors to consider if stop vs continue decision:
  - Consequences of virologic relapse
  - Burden of continued treatment (adherence, cost, monitoring)
  - Patient & provider preference
- If stop therapy, necessitates close monitoring of HBV DNA and ALT every 3 mos for at least a year

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault N, Hepatology 2016;63;261-83
## Durability of Response After Stopping Therapy in HBeAg-Negative Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>No</th>
<th>Rx</th>
<th>Rx Duration (Yrs)</th>
<th>F/U (Yrs)</th>
<th>Virological Relapse</th>
<th>Clinical Relapse</th>
<th>HBsAg loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeng</td>
<td>95</td>
<td>ETV</td>
<td>2</td>
<td>1</td>
<td>58%</td>
<td>45%</td>
<td>0%</td>
</tr>
<tr>
<td>Seto</td>
<td>184</td>
<td>ETV</td>
<td>3</td>
<td>1</td>
<td>91%</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>Kim</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patwardhan</td>
<td>33</td>
<td>LMV, ADV ETV, TDF</td>
<td>5</td>
<td>3</td>
<td>63%</td>
<td>33%</td>
<td>3%</td>
</tr>
<tr>
<td>Chi</td>
<td>59</td>
<td>LMV, ADV ETV, TDF, TBV</td>
<td>5</td>
<td>3</td>
<td>49%</td>
<td>--</td>
<td>14%</td>
</tr>
</tbody>
</table>

Few cases of relapse associated with hepatic decompensation

Virological relapse: HBV DNA >2,000 IU/mL
Clinical relapse: HBV DNA >2,000 IU/mL and ALT flare >2 xULN

Chi, Aliment Pharmacol Ther. 2015 May;41(9):867-76.
5-Year Follow-Up After Discontinuing Long-Term Adefovir Therapy

N=33

- All genotype D, no cirrhosis
- Treated with adefovir for 4 or 5 years
- 55% did not have clinical relapse and 13 lost HBsAg

Hadziyannis S et al, Gastro 2012;143:629-36
Chronic Hepatitis B Final Points

- Chronic HBV is common among foreign-born; screening to identify patients is critical
- Chronic HBV is dynamic disease, requiring life-long monitoring
- HBV is controlled not cured – long term treatment plan needed
- Target group for treatment are those with active disease and/or advanced fibrosis
- Tenofovir (TDF/TAF), entecavir and peg-IFN are preferred drugs
- Endpoints of treatment evolving → HBsAg is highly desirable but infrequently obtained
Thank-you