Beyond the Tip of the Iceberg: Strategies to Ensure Optimal HBV Screening, Diagnosis, and Initial Therapy

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Boston, Massachusetts

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Burden of Chronic HBV Disease

- ~ 400 million people worldwide living with chronic HBV infection
  - Yearly, ~ 500,000 people die of HBV-related cirrhosis and HCC
  - > 1 million US residents have chronic HBV infection
    - Up to two thirds are unaware of their infection
    - Less than one half of patients with known HBV infection referred to specialist for evaluation

To reduce disease complications, need to
- Identify infected individuals
- Assess disease status and need for treatment and other monitoring
- Optimize treatment outcomes: issues of who, when, and how to treat

3. CDC. MMWR. 2007;56:446-448.
HBV Screening and Diagnosis: Are Current Practices Effective at Identifying Patients at Risk and Evaluating Patients for HBV Treatment?

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Associate Professor of Medicine
Division of Gastroenterology and Hepatology
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Rochester, Minnesota
2008 CDC Guidelines for HBV Screening: New Recommendations

- Persons born in countries with ≥ 2% HBsAg prevalence
- US-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (≥ 8% HBsAg prevalence)
- Persons with behavioral exposures to HBV
  - Injection drug users, MSM
- Persons needing immunosuppressive therapy
  - Chemotherapy, organ transplantation, immunosuppression for rheumatologic or gastroenterologic disorders
- Persons with elevated ALT/AST of unknown etiology

http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm
Global Distribution of HBV

Prevalence of HBsAg
- High ≥ 8%
- Intermediate 2% to 7%
- Low < 2%

Centers for Disease Control and Prevention. CDC Health Information for International Travel 2010.
New HBV Cases Diagnosed in Olmsted County, Minnesota: 1994-2000

Noninvasive Assessment of Fibrosis

- No large-scale validation specific to hepatitis B patients
- Elastography data (n = 173)
  - Liver stiffness measure able to detect significant cirrhosis and fibrosis
    - Correlation with METAVIR and Ishak scoring systems demonstrated ($P < .001$)
  - Optimal cutoff for cirrhosis: 11.0 kPa
  - Sensitivity: 93%  
    - Specificity: 87%

Liver Stiffness in Acute Hepatitis

- Acute hepatitis without obvious evidence of chronic liver disease
- 18 total patients; 8 with HBV infection

Serum Markers of Fibrosis in Hepatitis B

**FibroTest**

AUROC: *FibroTest* = 0.78


**APRI vs LSM**

AUROC: LSM = 0.84, APRI = 0.78

HCC Surveillance: AASLD Practice Guideline Recommendations

- **Hepatitis B**
  - Cirrhosis regardless of age
  - Asian males 40 yrs of age or older
  - Asian females 50 yrs of age or older
  - HCC in first-degree relative (start before 40 yrs of age)
  - African older than 20 yrs of age

- **Cirrhosis from other causes**

Risk of HCC According to Baseline Factors

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

Surveillance Interval

- Optimal interval not known
- Randomized trial: decreased mortality based on 6-mo surveillance intervals (vs no screening)\(^1\)
- Retrospective data: equivalence between 6- and 12-mo intervals\(^2\)

Take Home Points

- HBV screening in the target population highly justified
  - Data indicate correlation between HBV DNA and long-term outcome
  - Antiviral therapy able to alter natural history

- Target population
  - Patients from areas with projected prevalence 2% or higher including unvaccinated US born children of immigrants from endemic areas

- Other groups
  - Immunosuppressive therapy
  - Abnormal aminotransferases
Take Home Points (cont’d)

Emerging data on noninvasive markers of fibrosis in HBV
- LSM probably more accurate than existing serum panel
- Acute flare may lead to false elevations of LSM

Cirrhosis is by far the largest risk factor for HCC

Correlation between HBV DNA and HCC risk well known
- Uncertain how that info is incorporated into surveillance strategy
After Diagnosis:
Given the Benefits of HBV Treatment, Why Do So Few Patients Initiate Therapy When Indicated?

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Director of Hepatitis Research
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New York, New York
### Treatment Criteria for Chronic Hepatitis B

#### Recommended HBV DNA and ALT levels outlined in the following table

<table>
<thead>
<tr>
<th>Liver Society Guidelines*</th>
<th>HBeAg Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA, IU/mL</td>
<td>ALT</td>
</tr>
<tr>
<td>APASL 2008[2]</td>
<td>≥ 20,000</td>
<td>&gt; 2 x ULN†</td>
</tr>
<tr>
<td>AASLD 2009[3]</td>
<td>&gt; 20,000</td>
<td>&gt; 2 x ULN† or (+) biopsy</td>
</tr>
</tbody>
</table>

*Although ALT and HBV DNA are primary tests used to determine treatment candidacy, the levels of elevation that warrant consideration of treatment are not universally agreed upon.

†Laboratory normal.

‡30 U/L for men and 19 U/L for women.

**In patients older than 40 yrs of age, 2000 IU/mL should be considered as a cutoff for treatment.

What Is a “Normal” ALT Level?

- 9221 first-time potential blood donors
- 74% suitable donors after exclusion of anemia, seizure, sexual, and other risk
  - 57% determined to be at “low risk” for liver disease
    - Negative viral serology
    - BMI < 25
    - Normal serum cholesterol, triglycerides, and glucose levels
    - Absence of concurrent medication use
- Updated healthy ALT ranges determined from the group of low-risk individuals
  - Males: 30 IU/L
  - Females: 19 IU/L

Beyond the Tip of the Iceberg
clinicaloptions.com/hepatitis

**Patients With Normal ALT May Have Significant Fibrosis**

- 1387 asymptomatic HBsAg-positive patients with ≥ 1-yr follow-up
  - 189 with persistently normal ALT (PNALT)* included in analysis (HBeAg negative: 116 / 189, 61%)
- 21% of HBeAg-negative patients with PNALT and HBV DNA < 5 log copies/mL had HAI ≥ 3 and/or fibrosis stage ≥ 2


*≥ 3 ALT values in the previous 1 yr prior to baseline liver biopsy that were all ≤ 40 IU/L and remained so until the start of treatment or the last follow-up.
Favorable Short-term Outcomes in Patients With High HBV DNA, Normal ALT

- 240 HBeAg-positive individuals (male 130, female 110); mean age: 27.6 yrs
- Mean follow-up: 10.5 yrs (range: 3-20)
- Spontaneous HBeAg seroconversion in 85% between the ages of 20 and 39 yrs
- Reactivation of hepatitis after HBeAg seroconversion in 2.2% per yr
- Progression to cirrhosis in 5.4% after 10 yrs
- HCC: none

Cumulative Risk of Liver-Related Complications in Chronic Hepatitis B

- Long-term follow-up of 3233 patients with chronic hepatitis B in Hong Kong
  - Risk of developing ascites, SBP, esophageal varices, encephalopathy, or HCC determined
  - Reference group: ALT < 0.5 x ULN
- Persons with ALT 0.5-1.0 x ULN and 1.0-2.0 x ULN had an increased risk of developing liver disease complications (P < .0001 vs reference group)

HBeAg-Negative Chronic HBV vs Inactive Carrier State

<table>
<thead>
<tr>
<th></th>
<th>HBeAg-Negative Disease</th>
<th>Inactive Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg positive</td>
<td>ü</td>
<td>ü</td>
</tr>
<tr>
<td>Anti-HBe positive</td>
<td>ü</td>
<td>ü</td>
</tr>
<tr>
<td>Anti-HBc positive</td>
<td>ü</td>
<td>ü</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>&gt; 2000 IU/mL*</td>
<td>&lt; 2000 IU/mL</td>
</tr>
<tr>
<td>ALT</td>
<td>Elevated†</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Fluctuations to < 2000 IU/mL can occur.
†May be elevated either persistently or intermittently.

HBeAg-Negative Patients Require Frequent Monitoring

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

Persistently Elevated HBV DNA Associated With Increased HCC Risk

* Cox proportional hazards models. Risk is relative to < 10^4 copies/mL at entry/not tested at follow-up. Data adjusted for sex, age, cigarette smoking, and alcohol consumption.

Take Home Points

- ALT is an imperfect measure of liver histology
  - “Normal” levels should be lower than the current reference range
- HBeAg-negative CHB patients require frequent monitoring
  - Severity of liver disease may not be evident from occasional testing
- Short-term outcome is favorable in CHB patients in immune-tolerant phase
- Active viral replication in CHB patients is associated with long-term risk of cirrhosis and HCC
Current Options for First-line HBV Treatment

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Goals of Hepatitis B Treatment

- Prevention of long-term negative clinical outcomes (e.g., cirrhosis, HCC, death) by durable suppression of HBV DNA

- Primary treatment endpoint
  - Sustained decrease in serum HBV DNA level to low or undetectable

- Secondary treatment endpoints
  - Decrease or normalize serum ALT
  - Improve liver histology
  - Induce HBeAg loss or seroconversion
  - Induce HBsAg loss or seroconversion
HBV Treatment Landscape in 2009

- Interferon alfa-2b (1990)
- Lamivudine (1998)
- Entecavir (2005)
- Tenofovir (2008)
- Adefovir (2002)
- Telbivudine (2006)
- Peginterferon alfa-2a (2002)
Factors Driving Selection of Initial Therapy

Nucleos(t)ide Analogues
- Safety & tolerability
- Efficacy (potency)
- Barrier to resistance (durability)

Peginterferon
- Safety & tolerability
- Efficacy (potency)
Undetectable* HBV DNA in HBV Patients After 1 Year of Treatment

*By PCR-based assay (LLD ~ 50 IU/mL) except for some LAM studies.

HBeAg Loss and Seroconversion in HBeAg+ Patients After 1 Year of Treatment

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

Cumulative Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generation</th>
<th>Yr 1</th>
<th>Yr 2</th>
<th>Yr 3</th>
<th>Yr 4</th>
<th>Yr 5</th>
<th>Yr 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM</td>
<td>1st</td>
<td>24%</td>
<td>38%</td>
<td>49%</td>
<td>67%</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>ADV</td>
<td>2nd</td>
<td>0%</td>
<td>3%</td>
<td>11%</td>
<td>18%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>TBV</td>
<td></td>
<td>4%</td>
<td>17%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETV</td>
<td>3rd</td>
<td>0.2%</td>
<td>0.5%</td>
<td>1.2%</td>
<td>1.2%</td>
<td>1.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>TDF</td>
<td></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1.2%</td>
<td>1.2%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Tolerability and Safety: Nucleos(t)ide Analogues vs Peginterferon

Nucleos(t)ide Analogues
- Safe at all stages of disease, including decompensated cirrhosis
- Safe in immunocompromised populations
  - Selected drugs probably safe in pregnancy
- Reported toxicities are rare

Peginterferon
- Contraindications
  - Decompensated cirrhosis
  - Pregnancy
  - Significant cardiopulmonary disease
  - Uncontrolled seizures, psychiatric disease
  - Autoimmune diseases
- Not recommended
  - Cirrhosis
- Adverse effects common

Current Guideline Recommendations for First-line Therapy

- Peginterferon alfa-2a
  - Exceptions: pregnancy, chemotherapy prophylaxis, decompensated cirrhosis
- Entecavir
- Tenofovir

HBeAg Seroconversion Rates Over Time in HBeAg-Positive Patients

*With sustained undetectable HBV DNA.


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

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

<table>
<thead>
<tr>
<th>Time</th>
<th>Entecavir</th>
<th>Tenofovir</th>
<th>Peginterferon</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 Yr</td>
<td>21</td>
<td>22</td>
<td>22-27</td>
</tr>
<tr>
<td>1.5-2.0 Yrs</td>
<td>31</td>
<td>26</td>
<td>29-32</td>
</tr>
<tr>
<td>3.0-4.0 Yrs</td>
<td>39</td>
<td>26</td>
<td>35</td>
</tr>
</tbody>
</table>
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 Limited Duration (1 Yr) Peginterferon Treatment

<table>
<thead>
<tr>
<th>Duration</th>
<th>Entecavir</th>
<th>Tenofovir</th>
<th>Peginterferon</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 Yr</td>
<td>2%</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>1.5-2.0 Yrs</td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>3.0-4.0 Yrs</td>
<td>NA</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*With sustained undetectable HBV DNA.

Predictors of HBsAg Loss in HBeAg-Positive Patients

- Race: whites > nonwhites[1]
- Genotype[1-3]
  - Nucleos(t)ide analogues: A and D
  - Peginterferon: A
- Decline in HBsAg level during first 24 wks with nucleos(t)ide analogues[1]
- HBeAg negative at or within 26 wks of completing peginterferon treatment[3]

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 Limited Duration (1 Yr) Peginterferon Treatment

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

*single center study.

HBsAg Loss Over Time in HBeAg-Negative Patients

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

On Extended Treatment With Nucleos(t)ide Analogues* vs Limited Duration (1 yr) Peginterferon Treatment

- Entecavir
- Tenofovir
- Peginterferon

*With sustained undetectable HBV DNA.

Wk 12 HBsAg Levels Predict Outcomes in HBeAg-negative Patients

- 48 patients consecutively treated with pegIFN alfa-2a for 48 weeks
- SVR defined as undetectable serum HBV DNA (< 70 copies/mL) 24 weeks after treatment cessation
- Change in HBsAg level from baseline to Week 12 evaluated as predictor of SVR
  - Cutoff of $0.5 \log_{10}$ IU/mL used
  - PPV = 89% – NPV = 90%

<table>
<thead>
<tr>
<th>Outcome, % (n)</th>
<th>Change in HBsAg from Baseline to Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\geq 0.5 \log_{10}$ IU/mL (n = 9)</td>
</tr>
<tr>
<td>SVR</td>
<td>89 (8)</td>
</tr>
<tr>
<td>No SVR</td>
<td>11 (1)</td>
</tr>
<tr>
<td></td>
<td>$&lt; 0.5 \log_{10}$ IU/mL (n = 39)</td>
</tr>
<tr>
<td></td>
<td>10 (4)</td>
</tr>
<tr>
<td></td>
<td>90 (35)</td>
</tr>
</tbody>
</table>

Summary of Therapy for CHB in Treatment-Naive Patients

- Tenofovir, entecavir, and peginterferon are preferred first-line drugs
  - First decision is between NAs vs peginterferon
  - 3rd generation NAs have high efficacy, very low rates of resistance, and excellent safety record
  - Peginterferon offers finite therapy, some evidence of off-treatment benefits

- HBeAg seroconversion
  - Increases over time with NAs
  - Approximately same after 3 yrs continuous treatment with NAs vs 1 yr of peginterferon

- HBsAg loss
  - Infrequent and increases slowly (< 10% at 3-4 yrs)
    - Rare in HBeAg-negative CHB with NAs
  - After 3-4 yrs follow-up, somewhat higher with peginterferon than NAs
Tip of the Iceberg:
Is Determining “How to Treat” a Barrier to Initiating HBV Therapy?

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Dean for Medical Education
Harvard Medical School
Physician, Gastrointestinal Unit
Massachusetts General Hospital
Boston, Massachusetts
The First Branch Point in Choosing Treatment for Hepatitis B

Decision to treat

PegIFN

Nucleos(t)ide analogues
Nucleos(t)ide Analogues vs PegIFN

- Use of pegIFN in younger patients
  - Very small proportion will benefit
  - Most will require longer treatment with nucleos(t)ide analogues
- PegIFN better in genotype A > B > C > D
  - Favorable genotypes growing vanishingly rare
  - This relationship between genotype and response seen for pegIFN alfa-2b but not with pegIFN alfa-2a
    - HBeAg seroconversion with pegIFN alfa-2a according to genotype
      - A: 52%; B: 30%; C: 31%; D: 22% (not significant)
- Predictors of HBeAg response same for pegIFN and nucleos(t)ide analogues (eg, high ALT, low HBV DNA)

Long-term Outcomes With pegIFN alfa-2a in HBeAg-Negative Chronic Hepatitis B

5 yrs posttreatment follow-up in patients treated with pegIFN ± LAM vs LAM alone for 48 wks

Outcomes With PegIFN ± LAM (n = 230 [65%] of original 356)

*vs 3.5% for LAM alone at Yr 5 (P = .022).

HBV DNA During Follow-up After Stopping Adefovir

- Patients receiving 4-5 years continuous adefovir followed long-term off treatment
  - 33 patients who had sustained undetectable HBV DNA on treatment followed
  - HBV DNA levels followed in 18 off-treatment sustained biochemical responders
- All patients initially rebounded to detectable HBV DNA
- Proportion of patients with HBV DNA < 1000 copies/mL
  - 1 month after adefovir discontinuation: 5.6%
  - 12 months after adefovir discontinuation: 55.6%
  - 48 months after adefovir discontinuation: 66.7%

HBsAg Loss Off Treatment After 4-5 Years of Continuous Adefovir

“Undesirable” Virologic Responses to Oral Therapy

Change in HBV DNA (log_{10} IU/mL)

-4.0 -3.0 -2.0 -1.0 0

0 6 12 18 Mo

Primary nonresponse
Suboptimal response
Nadir
Virologic breakthrough
1 log

Antiviral Drug

Does the Roadmap Concept Apply to ETV or TDF During First Yr?

- 1.2% resistance to ETV at 6 yrs in nucleos(t)ide-naive patients\(^1\)
- No resistance to TDF seen to date through 3 yrs in HBeAg-negative patients and 2 yrs in HBeAg-positive patients\(^2,3\)
  - Patients with positive HBV DNA at 24 and 48 wks often negative subsequently
- Tentative conclusion: for patients with positive HBV DNA at 48 wks on ETV or TDF, it may still be appropriate to continue monotherapy—especially if HBV DNA is still declining
- More data needed

Take Home Points

- For pegIFN: finite treatment for 48 wks
  - Some consider in young, noncirrhotic patients with low HBV DNA, high ALT, favorable genotypes

- For nucleos(t)ide analogues
  - Select entecavir or tenofovir in most cases
  - HBeAg-positive chronic hepatitis B: treat until HBeAg seroconversion, stop after consolidation period
  - HBeAg-negative chronic hepatitis B: treat indefinitely
Take Home Points (cont’d)

- In the case of incomplete response to entecavir or tenofovir
  - Distinguish between noncompliance, breakthrough resistance, and suboptimal response
  - “Roadmap” approach does not apply well
  - Suboptimal response: approach remains to be defined
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