Management of Chronic Hepatitis B in Asian Americans

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# Prevalence of HBsAg in Asian Americans and their respective native countries

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Country of Origin(%)</th>
<th>USA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>7.7-10.8</td>
<td>8-13</td>
</tr>
<tr>
<td>China</td>
<td>7.2</td>
<td>10-17</td>
</tr>
<tr>
<td>India</td>
<td>1.4-3</td>
<td>1-6</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2.3-3</td>
<td>7-10</td>
</tr>
<tr>
<td>Japan</td>
<td>0.8</td>
<td>0.6-1.1</td>
</tr>
<tr>
<td>Korea</td>
<td>3.7-5.7</td>
<td>10-13</td>
</tr>
<tr>
<td>Malaysia</td>
<td>3-5</td>
<td>7-10</td>
</tr>
<tr>
<td>Philippines</td>
<td>5-16</td>
<td>4.2-9</td>
</tr>
<tr>
<td>Thailand</td>
<td>&gt;8</td>
<td>1.5-10</td>
</tr>
<tr>
<td>Vietnam</td>
<td>10-16</td>
<td>6-18</td>
</tr>
</tbody>
</table>

Tong et al: *Dig Dis Sci* 2011
The Five Phases of Chronic Hepatitis B

HBsAg+

HBeAg+

anti-HBe+

Immune Tolerant

Immune Activation

Low Replicative

 Reactivation

Remission

Minimal Inflammation

Active Inflammation

Mild Inflammation

Active Inflammation

Inactive

PCM / BCPM Reactivation

Wild Type Reactivation
Occult CHB
The Clinical Stages of Chronic Hepatitis B
(Based on HBeAg, ALT and HBV DNA)

- Immune Tolerant
  - HBeAg+ Normal ALT DNA ++++
  - HBeAg+ Elevated ALT DNA +++
  - HBeAg+ Elevated ALT DNA ++
    - Albumin
    - Platelets

- Inactive Carrier
  - HBeAg- Normal ALT DNA + / -
  - HBeAg- Elevated ALT DNA +++

- Chronic Hepatitis
  - ALT: Alanine Aminotransferase
  - HBV DNA: Hepatitis B Viral DNA

- Cirrhosis
  - Albumin
  - Platelets

Tong et al: Hepatol Int 2010
Natural History Study of CHB Patients in the USA

- 1989-1999: 369 patients enrolled in a prospective study
- Followed for a mean of 84 months (7 years)
- Baseline laboratory tests: HBeAg, albumin, ALT, Platelets, DNA HBV
- HCC surveillance: AFP and abdominal ultrasound
- Mean age at recruitment: 48 years; 79% Asian
- Mean follow-up 84 months:
  - 37 died non-HCC liver deaths
  - 30 developed HCC
### Independent Factors Associated with Disease Progression

<table>
<thead>
<tr>
<th>Non-HCC Liver Deaths</th>
<th>OR</th>
<th>HCC</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older Age</td>
<td>96</td>
<td>Older Age</td>
<td>26</td>
</tr>
<tr>
<td>Male Sex</td>
<td>7.6</td>
<td>Male Sex</td>
<td>6.5</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>14</td>
<td>Cirrhosis</td>
<td>3.6</td>
</tr>
<tr>
<td>HBeAg+</td>
<td>3.4</td>
<td>HBeAg-</td>
<td>2.3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>1.2</td>
<td>Decreased ALT</td>
<td>1.4</td>
</tr>
<tr>
<td>Increased HBV DNA</td>
<td>4.7</td>
<td>Increase AFP</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Reduced Albumin</strong></td>
<td>69</td>
<td><strong>Precore Mutant</strong></td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Reduced Platelets</strong></td>
<td>8.8</td>
<td><strong>Basal Core Promoter Mutant</strong></td>
<td>11</td>
</tr>
</tbody>
</table>

Treatment Guidelines for CHB

• EASL, US Panel, Asian-Pacific Panel, AASLD
• Treatment based on levels of ALT, HBV DNA, and HBeAg in the setting of chronic hepatitis or cirrhosis
• Controversies:
  – ALT*, HBV DNA levels differ in 4 guidelines
  – Not evidenced based and may omit patients who die from liver disease or develop HCC

## CHB Treatment Criteria

<table>
<thead>
<tr>
<th>Guideline</th>
<th>HBeAg+</th>
<th></th>
<th>HBeAg-</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA (IU/mL)</td>
<td>ALT (U/L)</td>
<td>HBV DNA (IU/mL)</td>
<td>ALT (U/L)</td>
</tr>
<tr>
<td>EASL 2008</td>
<td>≥2000</td>
<td>&gt;ULN&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≥2000</td>
<td>&gt;ULN&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>US Algorithm 2008</td>
<td>≥20,000</td>
<td>&gt;ULN&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥2000</td>
<td>&gt;ULN&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>APASL 2008</td>
<td>≥20,000</td>
<td>&gt;2x ULN&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥20,000</td>
<td>&gt;2x ULN&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AASLD 2009</td>
<td>≥20,000</td>
<td>&gt;2x ULN&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥2000</td>
<td>&gt;2x ULN&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


<sup>c</sup> ULN for EASL 31 IU/ml (men) and 19 (women) Tong, discussion with EASL Guideline author Marcellin. EASL. *J Hepatol.* 2009;50:227-242.
Evaluation of Current Treatment Guidelines Based on a Natural History Study in the USA

- Criteria for treatment from 4 guidelines (HBeAg, ALT, HBV DNA) for chronic hepatitis and cirrhosis were matched with tests from 369 HBsAg+ patients.
- Objective was to determine if criteria for antiviral therapy in the 4 guidelines included patients who died from non-HCC liver related complications or who developed HCC.
- The new ALT values and HBV DNA levels suggested by the 4 guidelines were used to determine eligibility for antiviral therapy in our HBsAg+ patients.
Evaluation of Existing CHB Treatment Algorithms and Guidelines

369 CHB patients, predominantly Asians, in a US community clinic, followed for a mean of 84 months (7 years).

<table>
<thead>
<tr>
<th></th>
<th>EASL</th>
<th>US Algorithm</th>
<th>APASL</th>
<th>AASLD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-HCC Liver-related Deaths</strong> <em>(N = 37)</em> # and (%) recommended for treatment based on HBV DNA and ALT</td>
<td>30 (81%)</td>
<td>26 (70%)</td>
<td>26 (70%)</td>
<td>26 (70%)</td>
</tr>
<tr>
<td><strong>HCC</strong> <em>(N = 30)</em> # and (%) recommended for treatment based on HBV DNA and ALT</td>
<td>23 (77%)</td>
<td>20 (67%)</td>
<td>14 (47%)</td>
<td>16 (53%)</td>
</tr>
</tbody>
</table>

## Impact of Including Additional Treatment Parameters

<table>
<thead>
<tr>
<th>Patients who died from cirrhosis or who developed HCC (N = 67)</th>
<th>EASL</th>
<th>US Algorithm</th>
<th>APASL</th>
<th>AASLD</th>
</tr>
</thead>
<tbody>
<tr>
<td># and % recommended for treatment based on additional parameters:</td>
<td>63 (94.0%)</td>
<td>61 (91%)</td>
<td>57 (85.1%)</td>
<td>58 (86.6%)</td>
</tr>
<tr>
<td>• albumin ≤3.5 g/dL,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• platelets ≤ 130,000 mm$^3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># and % recommended for treatment based on additional parameters:</td>
<td>67 (100%)</td>
<td>67 (100%)</td>
<td>66 (98.5%)</td>
<td>66 (98.5%)</td>
</tr>
<tr>
<td>• albumin ≤3.5 g/dL,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• platelets ≤ 130,000 mm$^3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• basal core or precore mutant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Asian American Treatment Algorithm: Recommendations for CHB Treatment

- **Treat with antiviral treatment:**
  - *HBeAg+ or HBeAg- chronic hepatitis*
    - HBV DNA >2,000 IU/ml
    - ALT > ULN (of the clinical laboratory)
    - Liver biopsy grade 1-3 and/or stage 1-3
  - *HBeAg+ or HBeAg- cirrhosis*
    - Any detectable HBV DNA (regardless of ALT level)
  - *HBeAg+ or HBeAg- decompensated cirrhosis*

- **Monitor only, no treatment:**
  - *HBeAg+ Immune tolerant*
  - *HBeAg- Inactive carrier*
  - *HBeAg+ or HBeAg- compensated cirrhosis with undetectable HBV DNA*

Tong et al: *Dig Dis Sci* 2011
Asian American Treatment Algorithm: Recommendations for CHB Treatment

• **Patients in the gray zone - assess for antiviral therapy:**
  – **HBeAg- chronic hepatitis**
    • HBV DNA >2000 IU/mL, ALT ≤ULN (of the clinical laboratory)
  – **HBeAg +/- chronic hepatitis**
    • HBV DNA ≤2000 IU/mL, ALT >ULN (of the clinical laboratory)
  – **Assess for antiviral therapy**
    • Liver biopsy if available; if not, use Risk Impact Score

Tong et al: *Dig Dis Sci* 2011
Evaluation of CHB Patients in the Gray Zone: Risk Impact Score

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Impact Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥40 years</td>
<td>1</td>
</tr>
<tr>
<td>Male gender</td>
<td>1</td>
</tr>
<tr>
<td>ALT Male ≥30 U/L or Female ≥19 U/L</td>
<td>1</td>
</tr>
<tr>
<td>Basal core promoter mutation (BCPM)</td>
<td>2</td>
</tr>
<tr>
<td>HCC in first degree relative</td>
<td>3</td>
</tr>
<tr>
<td>Albumin ≤3.5 g/dL or platelet count ≤130,000 mm³</td>
<td>3</td>
</tr>
</tbody>
</table>

**Recommend Treatment**

- HBV DNA ≤2000 IU/mL
- HBV DNA >2000 IU/mL

Monitor without treatment

Tong et al: *Dig Dis Sci* 2011
# Summary of Treatment Candidate Selection Based on Clinical Stage, HBeAg, HBV DNA and Serum ALT

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Tolerant</td>
<td>+</td>
<td>&gt;2000 IU/ml</td>
<td>≤ULN</td>
<td>Monitor</td>
</tr>
<tr>
<td>Chronic Hepatitis&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>+</td>
<td>&gt;2000 IU/ml</td>
<td>&gt;ULN</td>
<td>Treat</td>
</tr>
<tr>
<td>Chronic Hepatitis&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>-</td>
<td>&gt;2000 IU/ml</td>
<td>&gt;ULN</td>
<td>Treat</td>
</tr>
<tr>
<td>Chronic Hepatitis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>&gt;2000 IU/ml</td>
<td>≤ULN</td>
<td>Assess gray zone considerations</td>
</tr>
<tr>
<td>Chronic Hepatitis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+/-</td>
<td>≤2000 IU/ml</td>
<td>&gt;ULN</td>
<td>Assess gray zone considerations</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>+/-</td>
<td>Detectable</td>
<td>NA</td>
<td>Treat</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>+/-</td>
<td>Undetectable</td>
<td>NA</td>
<td>Monitor</td>
</tr>
<tr>
<td>Decompensated Cirrhosis</td>
<td>+/-</td>
<td>NA</td>
<td>NA</td>
<td>Treat</td>
</tr>
<tr>
<td>Inactive Carrier</td>
<td>-</td>
<td>≤2000 IU/ml</td>
<td>≤ULN</td>
<td>Monitor</td>
</tr>
</tbody>
</table>

<sup>a</sup> or liver biopsy stage 1-3 and/or grade 1-3; <sup>b</sup> ALT normal range is based on local laboratory reference range; ULN: upper limit of normal. NA: not applicable.
Asian American Treatment Algorithm: Recommendations for CHB Treatment

- Tenofovir and entecavir are the two recommended first-line agents for treatment in Asian American CHB patients
  - Because of cross-resistance issues, entecavir is not recommended in patients with lamivudine resistance
- The use of pegylated interferon alfa-2a is a consideration if a finite period of treatment is desired.
  - Interferon is contraindicated in patients with decompensated cirrhosis

Oral Antiviral Agents for CHB: Development of Drug Resistance in treatment-naïve Asian patients

<table>
<thead>
<tr>
<th>Oral Antiviral Agents</th>
<th>Resistant Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>70% in 5 years</td>
</tr>
<tr>
<td>Adefovir</td>
<td>29% in 5 years</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>22% in 2 years</td>
</tr>
<tr>
<td>Entecavir</td>
<td>1.5% in 5 years</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>0% in 5 years</td>
</tr>
</tbody>
</table>

Marcellin et al. *AASLD* 2011
Management of Pre-Existing Mutations

- Preexisting mutations are detected in 7.5–28% of presumed treatment-naive patients.

- The majority of mutations identified in clinical studies were lamivudine, telbivudine, or adefovir signature mutations, suggesting that mutations occur spontaneously or the patients’ histories were not reliable.

- The management of resistance to oral antiviral agents includes obtaining a detailed treatment history and accurately interpreting drug-mutation analysis before choosing a new antiviral regimen.
Monitoring of CHB Patients on Treatment

- HBV DNA q3 months until undetectable; then q3-6 months
- ALT q3 months until within normal limits; then q3-6 months
- HBeAg positive patients:
  - HBeAg q6 months until negative; then initiate testing for anti-HBe
  - HBsAg q12 months after HBeAg seroconversion

Monitoring of CHB Patients on Treatment

- HBeAg negative patients:
  - HBsAg q12 months after sustained suppression of HBV DNA
- Renal monitoring may be necessary in patients receiving adefovir
- CBC q2-4 weeks and thyroid function test in patients receiving pegylated interferon therapy

Management of Antiviral Resistance & Suboptimal Response

• Single drug genotypic resistance
  – Drug resistance to lamivudine, adefovir, telbivudine or entecavir: switch to tenofovir or tenofovir + entecavir
  – Drug resistance to adefovir: switch to tenofovir or entecavir or tenofovir + entecavir. In patients with renal dysfunction on adefovir, entecavir is preferred.

• Multidrug genotypic resistance
  – Combination of entecavir + tenofovir
  – Pegylated interferon alpha 2a

When to Stop Treatment in HBeAg+ patients

- Patients with HBeAg+ CHB:
  - Treat until seroconversion to anti-HBe positive
  - Continue with “consolidation therapy” for 1-2 years
  - After stopping therapy, monitor for relapse (seroreversion to HBeAg positivity, reappearance of HBV DNA and ALT elevation)

When to Stop Treatment in HBeAg+ patients

• Patients with HBeAg- CHB:
  – Continue antiviral treatment indefinitely
  – If HBsAg becomes negative, then treatment may be stopped
    • Monitor closely for relapse

• Patients with cirrhosis:
  – Continue antiviral treatment for life

Special Populations: HBV Coinfection with HCV, HDV, or HIV

- All three co-infections may hasten progression of liver disease
- HCV: peg-interferon + ribavirin + oral antiviral agent
- HDV: peg-interferon
- HIV: special considerations depending if patient requires HAART

In the US all pregnant women are screened for HBsAg.

- If positive, the infants are treated with HBIG and HBV vaccine series, with 1st dose HBV vaccine within 12 hours of birth.

However, 7% - 37% of infants fail immunoprophylaxis, especially those born to HBeAg positive mothers with HBV DNA \( \geq 6 \log_{10} \) copies/ml.

- Consider oral antiviral during 3rd trimester of pregnancy:
  - Mothers with HBV DNA \( \geq 6 \log_{10} \) copies/ml
  - Previous infants who failed immunoprophylaxis after birth

Special Populations: Reactivation During Chemotherapy or Immunosuppressive Therapy

- Screen Asian patients for HBsAg prior to chemotherapy or immunosuppressive therapy (steroids, rituximab), or those receiving bone marrow transplantation.

- Treat all HBsAg-positive patients with oral antiviral agent for prophylaxis.

- Anti-HBc positive patients who had HBsAg loss and persons positive for both anti-HBc and anti-HBs should be considered for therapy.

## HCC Surveillance in Asian Americans with CHB

| Surveillance Tests | • Alfa-fetoprotein  
<table>
<thead>
<tr>
<th></th>
<th>• Abdominal ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance Interval</td>
<td>• Every 6 months</td>
</tr>
</tbody>
</table>
| Surveillance Candidates | • High-risk patients  
|                     |   – Cirrhosis  
|                     |   – HCC in blood relatives |
|                     | • Low- to moderate-risk patients  
|                     |   – Inactive carriers  
|                     |   – Immune-tolerant patients  
|                     |   – HBsAg+ males <40 years, females <50 years  
|                     |   – Patients with HBsAg loss  
|                     |   (especially cirrhosis patients) |

Summary of Recommendations: Management of CHB in Asian Americans

1) *First line agents*: For HBeAg-positive or negative patients, treat with entecavir or tenofovir
   - when HBV DNA is \( >2000 \text{ IU/ml} \) and \( \text{ALT} > \text{ULN} \) based on local reference lab.

2) *Cirrhotic patients*: If detectable HBV DNA, treat with entecavir or tenofovir, regardless of ALT level.

3) *HBeAg-negative patients with HBV DNA >2,000 IU/mL and normal ALT*. Stratified risk with:
   - **liver biopsy** (treat if \( \geq \) grade 1 or stage 1) or
   - **risk impact score** (treat if score \( \geq 3 \) and HBV DNA > 2000 IU/ml).

Tong et al: *Dig Dis Sci*: 2011
Summary of Recommendations: Management of CHB in Asian Americans

4) **Monitoring during treatment:**
   - Check ALT and HBV DNA q3 months until normal / undetectable, then q3-6 months.
   - In HBeAg+ patients, check HBeAg q6 months until (-), then check for anti-HBe.

5) **HBsAg monitoring:**
   - In HBeAg+, after HBeAg seroconversion, test for HBsAg q12 months.
   - In HBeAg-, test for HBsAg q12 months after sustained HBV DNA suppression.

6) **Monitoring of resistance:** Viral breakthrough with confirmed single drug resistance requires switching to another first line oral antiviral agent.

Tong et al: *Dig Dis Sci*: 2011
Summary of Recommendations: Management of CHB in Asian Americans

7) **HCC surveillance**: Surveillance should be performed every 6 months in patients with chronic hepatitis, cirrhosis or family history of HCC.

8) **Pregnancy**: HBsAg-positive mothers should be tested for HBV DNA. If HBV DNA is \( \geq 10^6 \) copies/ml, consider using antiviral agent during 3rd of pregnancy.
   - Avoid breast feeding if mothers are on antiviral treatment.

9) **Immunosuppression**: HBsAg-positive patients requiring chemotherapy or immunosuppressive therapy should receive antiviral therapy.

Tong et al: *Dig Dis Sci*: 2011