HBV: Update and Treatment Guidelines

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Learning Objective

• Identify the appropriate therapy for patients with chronic hepatitis B infection
Outline

• Introduction
• Treatment Indications
• Goals of Therapy
• Treatment Options
• Choosing Appropriate Therapy
• On Treatment Management Considerations

Hepatitis B

• The most common hepatitis virus worldwide
• Transmission: Perinatal, close contact during childhood, IV drug use, and sexual
• Clinical course and chronicity vary with age of exposure
• Outcomes: Cirrhosis, hepatocellular carcinoma, and liver related mortality
### Phases of CHB Infection

<table>
<thead>
<tr>
<th></th>
<th>ALT</th>
<th>HBV DNA</th>
<th>HBeAg</th>
<th>Liver Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune tolerant</td>
<td>Normal</td>
<td>Elevated</td>
<td>Pos</td>
<td>Minimal inflammation and fibrosis</td>
</tr>
<tr>
<td><strong>HBeAg Positive</strong></td>
<td>Elevated</td>
<td>Elevated</td>
<td>Pos</td>
<td>Moderate to severe inflammation or fibrosis</td>
</tr>
<tr>
<td><strong>immune active</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive CHB</td>
<td>Normal</td>
<td>Low or undetectable</td>
<td>Neg</td>
<td>Minimal necroinflammation but variable fibrosis</td>
</tr>
<tr>
<td><strong>HBeAg-negative</strong></td>
<td>Elevated</td>
<td>Elevated</td>
<td>Neg</td>
<td>Moderate to severe inflammation or fibrosis</td>
</tr>
<tr>
<td><strong>immune reactivation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Treatment Indications

*Antiviral therapy is recommended for adults with immune-active chronic hepatitis B to decrease risk of liver related complications*

Quality of Evidence: Moderate  
Strength of Recommendation: Strong

AASLD Guidelines for Treatment of Chronic Hepatitis B  
Terrault et al Hepatology 2015
HBe Ag positive CHB – Immune Active

- **ALT**
  - Elevated >2x ULN
    - Men: ALT >30
    - Women: ALT >19

- **HBV DNA**
  - Elevated
    - ≥20,000 IU/mL

- **HBe Ag**
  - Positive

- **Histology**
  - Moderate to Severe Inflammation or Fibrosis

- **Duration**
  - Highly variable

HBe Ag Negative CHB – Immune Active

- **ALT**
  - Elevated >2x ULN

- **HBV DNA**
  - Elevated
    - ≥2000 IU/mL

- **HBe Ag**
  - Negative

- **Histology**
  - Moderate to Severe Inflammation or Fibrosis

- **Duration**
  - Highly variable
Treatment “Gray Zone”

- **Immune Tolerant**
  - ALT normal
  - DNA high
  - No Treatment

- **Immune Active**
  - ALT 2X ULN
  - DNA threshold met
  - Treatment

**Factors to consider**

- Severity of liver disease by biopsy or non-invasive testing
- Age >40 has increased risk of histological disease
- Family history of HCC
- Presence of extra hepatic manifestations
- Previous treatment history
First Line Treatment Options

Peg-IFN, entecavir, or tenofovir are the preferred initial therapies for adults with immune active CHB.

Quality of Evidence: Low
Strength of Recommendation: Strong

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault et al Hepatology 2015

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN</td>
<td>180 μg weekly</td>
<td>48 weeks</td>
<td>C</td>
</tr>
<tr>
<td>Entecavir</td>
<td>0.5 or 1 mg daily*</td>
<td>indefinite</td>
<td>C</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>300mg daily</td>
<td>indefinite</td>
<td>B</td>
</tr>
</tbody>
</table>

*Entecavir dose is 1 mg daily if lamivudine or telbivudine experienced
### Drug Potential Side Effects Monitoring on Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Side Effects</th>
<th>Monitoring on Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg-IFN</td>
<td>Flu like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders</td>
<td>CBC q 1-2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TSH q 3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical monitoring for side effects</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Lactic acidosis</td>
<td>Lactic acid level if clinical concern</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Nephropathy, Fanconi syndrome, Osteomalacia, lactic acidosis</td>
<td>Creatinine clearance at baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If at risk, Cr clearance, phosphate, urine glucose, and protein annually</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider bone density at baseline in persons at risk for osteopenia or history of fracture</td>
</tr>
</tbody>
</table>

**Goals of Therapy**

- Complete eradication of virus is not achievable (yet)

- Intermediate Outcomes are the endpoints for treatment
  - Undetectable levels of HBV DNA
  - Loss of HBe Ag and develop HBe Ab
  - Normal ALT
  - Improvement in liver histology

- Long term outcomes
  - Loss of HBsAg and development of HBsAb
  - Halt progression of liver inflammation to fibrosis, cirrhosis, or HCC
### PEG-IFN Efficacy in CHB

<table>
<thead>
<tr>
<th>%</th>
<th>HBe Ag Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA Suppression</td>
<td>30-42 &lt;2000-40,000 IU/mL</td>
<td>43 &lt;4,000 IU/mL</td>
</tr>
<tr>
<td></td>
<td>8-14 &lt;80 IU/mL</td>
<td>19 &lt;80 IU/mL</td>
</tr>
<tr>
<td>HBeAg Loss</td>
<td>32-36</td>
<td>-</td>
</tr>
<tr>
<td>HBeAg Seroconversion</td>
<td>29-36</td>
<td>-</td>
</tr>
<tr>
<td>Normalization of ALT</td>
<td>34-52</td>
<td>59</td>
</tr>
<tr>
<td>HBsAg Loss</td>
<td>6 months 2-7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3 years 11</td>
<td>6</td>
</tr>
</tbody>
</table>

Liaw YF et al; Hepatology; 2011;54:1591-1599

### Entecavir Efficacy in CHB

<table>
<thead>
<tr>
<th>%</th>
<th>HBe Ag Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA Suppression</td>
<td>61 &lt;50-60 IU/mL</td>
<td>90-91 &lt;50-60 IU/mL</td>
</tr>
<tr>
<td>HBeAg Loss</td>
<td>22-25</td>
<td>-</td>
</tr>
<tr>
<td>HBeAg Seroconversion</td>
<td>21-22</td>
<td>-</td>
</tr>
<tr>
<td>Normalization of ALT</td>
<td>68-81</td>
<td>78-88</td>
</tr>
<tr>
<td>HBsAg Loss</td>
<td>1 year 2-3</td>
<td>0-1</td>
</tr>
<tr>
<td></td>
<td>2 years 4-5</td>
<td></td>
</tr>
</tbody>
</table>

Lok AS et al Gastroenterology 2012; 143:619-628
Gish RG et al Gastroenterology 2007; 133:1437-1444
Tenofovir Efficacy in CHB

<table>
<thead>
<tr>
<th>%</th>
<th>HBe Ag Positive</th>
<th>HBeAg Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA Suppression</td>
<td>76 &lt;60 IU/mL</td>
<td>93 &lt;60 IU/mL</td>
</tr>
<tr>
<td>HBeAg Loss</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HBeAg Seroconversion</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>Normalization of ALT</td>
<td>68</td>
<td>76</td>
</tr>
<tr>
<td>HBsAg Loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>3 years</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Heathcote EJ et al Gastroenterology 2011; 140:132-143

CHB Treatment Decreases Liver Related Complications

- Reduces risk of **cirrhosis**
  - Observational studies: RR = 0.39 (95% CI: 0.2-0.75)
  - RCT: RR = 0.55 (95% CI: 0.38-0.78)
- Reduces risk of **HCC and Death**
  - Observational studies: RR = 0.49 (95% CI: 0.35-0.70)
  - Observational studies: RR = 0.6 (95% CI: 0.5-0.8)
- Reduces risk of **decompensation**
  - RCT: RR = 0.44 (95% CI: 0.29-.68)
- Reduces risk of **HCC and decompensation** in cirrhosis
  - RR = 0.54 (95% CI:0.41-0.72)
  - RR = 0.45 (95% CI: 0.22-0.89) Lok A et al Hepatology 2016
Should treatment be stopped if HBe Ab Develops?

- **HBeAg positive adults without cirrhosis with CHB who seroconvert to anti-HBe on therapy discontinue NAs after a period of treatment consolidation.**

- **Indefinite antiviral therapy is suggested in HBeAg positive adults with cirrhosis**

Quality of Evidence: Very Low  
Strength of Recommendation: Conditional

AASLD Guidelines for Treatment of Chronic Hepatitis B  
Terrault et al *Hepatology* 2015

**Medical Risk**
- Relapse
- Decompensation
- HCC
- Death

**Human Factors**
- Patient and provider preferences

**Burden of Care**
- Financial
- Monitoring
- Adherence
- Drug resistance

- Monitoring for ALT flares, viremia seroconversion, decompensation
- HCC screening continues
What is the duration of treatment in HBeAg Negative CHB?

**Indefinite** antiviral therapy for adults with HBeAg-negative immune active CHB, unless there is a competing rationale for discontinuation

Quality of Evidence: Low
Strength of Recommendation: Conditional

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault et al *Hepatology* 2015

Effect of Treatment Discontinuation

- ≈50% recurrent HBV viremia ≥2,000 IU/mL
- ≈33-50% had ALT elevation
- Liver decompensation events
  - 8.2, 12.5, 19.8% at 1,2,5 years
  - 3 deaths in cirrhotic patients

Fung SK et al *J Viral Hepat* 2004; 11:432-438
Liu F et al *J Gastroenterol Hepatol* 2011; 26:456-460
Hadziyannis SJ et al *Gastroenterology* 2012;143:629-636
Jeng WJF et al *Hepatology* 2013;58:1888-1896
Renal and Bone Health in Patients on NA Therapy

No preference between entecavir and tenofovir regarding potential long term risk of renal and bone complications

Quality of Evidence: Very Low (bone); Low (renal)
Strength of Recommendation: Conditional

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault et al Hepatology 2015

Renal and Bone Health

• Tenofovir has been associated with acute and chronic renal disease
• No differences in renal function seen in two short term RCT (48 wks)
• “Real world” cohorts have low incidence of renal and bone events (<2%)
• Hypophosphatemia and renal failure have been reported in tenofovir
Tenofovir requires renal monitoring

- Creatinine, phos, urine glucose, and urine protein at baseline and then annually depending on risk

- In absence of other risk factors for osteoporosis/osteomalacia, not enough evidence to support BMD monitoring

- Dosage of NAs should be adjusted based on renal function and CrCl

Management of Low Level Viremia

*Persistent low level viremia on entecavir or tenofovir monotherapy should continue monotherapy regardless of ALT*

Quality of Evidence: Very Low
Strength of Recommendation: Conditional

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault et al *Hepatology* 2015
Management of Low Level Viremia

- Persistent viremia is a plateau in decline and/or failure to be undetectable at 96 weeks

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault et al Hepatology 2015

Management of Viral Breakthrough

- Viral breakthrough
  - increase in HBV DNA ≥1 log compared to nadir
  - HBV DNA ≥100 IU/mL when previously <10 IU/mL

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Switch Strategy</th>
<th>Add Strategy: 2 Drugs without Cross-Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Tenofovir</td>
<td>Continue Lam; add Tenofovir Emtricitabine-Tenofovir</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Tenofovir</td>
<td>Continue Telbivudine; add Tenofovir</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Entecavir</td>
<td>Continue Adefovir; Add Entecavir</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Tenofovir</td>
<td>Continue Entecavir; add Tenofovir Emtricitabine-Tenofovir</td>
</tr>
<tr>
<td>Multi-drug</td>
<td>Tenofovir</td>
<td>Combined tenofovir and entecavir</td>
</tr>
</tbody>
</table>
Cirrhosis and Low Level Viremia

*Adults with compensated cirrhosis and low levels of viremia (≤2,000 IU/mL) should be treated with antiviral therapy to reduce the risk of decompensation*

Quality of Evidence: Very Low
Strength of Recommendation: Conditional

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault et al *Hepatology* 2015

Decompensated Cirrhosis

*HBsAg-positive adults should be treated with antiviral therapy indefinitely, regardless of HBV DNA level, HBeAg status or ALT, to decrease risk of worsening liver related complications*

Quality of Evidence: Moderate
Strength of Recommendation: Strong

AASLD Guidelines for Treatment of Chronic Hepatitis B
Terrault et al *Hepatology* 2015
Take Home Points

• Antiviral therapy is recommended for immune active CHB to decrease risk of liver related outcomes

• PEG-IFN, entecavir, or tenofovir are preferred initial therapy

• Individuals with cirrhosis should be treated regardless of ALT and considered for liver transplantation

• High quality data is lacking in several common clinical scenarios in the treatment of CHB