A Practical Approach to the Management of Hepatitis B

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The HBsAg (+) Patient

**The Patient**
- Exclude co-infection
  - HCV, HIV, HDV
- Immunize against HAV
- Screen for HCC
- Counsel on risk to others
  - Test and immunize close contacts
- Stress need for continued medical care

**The Infection**
1. Assess degree of viremia
   - Determine e-antigen status
   - Determine viral load
2. Assess for inflammation
   - Elevated liver enzymes or
   - Liver biopsy
3. Determine need for treatment
“Stage” the Infection

<table>
<thead>
<tr>
<th></th>
<th>ACTIVE</th>
<th>LOW REPLICATIVE</th>
<th>IMMUNE TOLERANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>Elevated</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>HBV-DNA</td>
<td>&gt;20,000 IU (eAg +)</td>
<td>&lt;2,000 IU</td>
<td>&gt;&gt;20,000,000 IU</td>
</tr>
<tr>
<td>&gt; 2,000 IU (eAg -)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Biopsy</td>
<td>Inflammation + fibrosis</td>
<td>No Inflammation + fibrosis</td>
<td>No inflammation + fibrosis</td>
</tr>
<tr>
<td>Approach</td>
<td>Treat</td>
<td>Do not Treat</td>
<td>Do not treat</td>
</tr>
</tbody>
</table>

Assessing Need for Therapy

1. **Inflammation**
   - Elevated ALT (> ULN or >20 ♂ / >30 ♀?)
   - Liver Biopsy – inflammation &/or fibrosis

2. **Viremia**
   - e-antigen (+) - >20,000 IU (100,000 copies)
   - e-antigen (-) - >2,000 IU (10,000 copies)

**Inflammation + Viremia = Treat**
The “I’m Not Too Sure What to Do” Patient

• Features that lower threshold for therapy

<table>
<thead>
<tr>
<th>Host Factors</th>
<th>Virus Factors</th>
<th>Environmental Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40*</td>
<td>High levels of HBV-DNA*</td>
<td>Concurrent infection</td>
</tr>
<tr>
<td>Male*</td>
<td>Genotype (C&gt;B)*</td>
<td>Alcohol use*</td>
</tr>
<tr>
<td>Immune status</td>
<td>HBV variant (core promoter)</td>
<td>Diabetes mellitus†</td>
</tr>
<tr>
<td>Family history HCC*</td>
<td></td>
<td>Obesity†</td>
</tr>
</tbody>
</table>

* Supported by strong evidence. †Further studies needed

Yim JY, Lok AS. Hepatology 2006;43:S173-S181

When in Doubt – Re-evaluate!

- Immune Tolerant
  - Observe

- Immune Active
  - Treat

- Low-replicative
  - Don’t Treat
The “I’ve Got To Treat This One!” Patient

- 20 years old female
  - Taiwanese
  - Asymptomatic
  - ALT 15
  - HBeAg (+)
- HBV-DNA 200 million

Study Population
- Male – 67%
- Age > 40y – 67%
- HBeAg (-) – 85%

REVEAL Study

Relative Risk of Cirrhosis

![Graph showing relative risk of cirrhosis]

Iloeje UH, et al. Gastroenterology 2006;130:678-686

The Immune Tolerant Patient

- Profile
  - Perinatal acquisition of infection
  - Young (< 30 years)
  - HBeAg (+), High viral load, often >20 million IUIU
  - Normal ALT (<30 males, <19 females)
  - Normal liver biopsy

Natural history
- No liver damage while immune tolerant
- Eventually most will develop active disease
  - Mean age 30.7 years

Current Guidelines Recommend NO Antiviral Therapy

DNA Levels Cannot be Interpreted in Isolation

More Likely to Treat
- Elevated ALT
- Inflammation, fibrosis, cirrhosis
- e-antigen (-)
- Age over 40
- Positive history
- Co-infection

DNA levels cannot be interpreted in isolation. Factors such as age, ALT, e-antigen, HIV/HCV, histology, family history, and liver disease (e.g., fibrosis, cirrhosis) are crucial in determining the likelihood of treatment.

FDA Approved Treatment Options

- **Interferons**
  - Interferon alfa-2b
  - Peginterferon alfa-2a
- **Nucleosides / Nucleotides**
  - Lamivudine
  - Adefovir dipivoxil
  - Entecavir
  - Telbivudine
  - Tenofovir
State of the Art HBV Therapy

**First Line Therapies**

- Tenofovir
- Entecavir
- Pegylated Interferon alfa-2a

**Tenofovir & Entecavir**

- Potent, once a day oral antivirals
  - On treatment >95% virus negative at 5 years
- High barrier to resistance at 5 yrs
  - entecavir ~1%
  - tenofovir 0%
- Excellent safety profile

Lok AS. Hepatology 2010;52:743-747
Marcellin, P, et al. AASLD 2011; Oral #238
### Antiviral Therapy Selection

<table>
<thead>
<tr>
<th>Entecavir</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not ideal in lamivudine experienced patients</td>
<td>Effective in lamivudine resistance</td>
</tr>
<tr>
<td>Effective in adeovir resistance or partial response</td>
<td>Less potent, but effective in adeovir genotypic resistance</td>
</tr>
<tr>
<td>Take on empty stomach</td>
<td>No food effect</td>
</tr>
<tr>
<td>Pregnancy class C</td>
<td>Pregnancy class B</td>
</tr>
</tbody>
</table>

### When to Stop Treatment

- **HBeAg (-) patients or HBV Cirrhosis**
  - Stop when HBsAg (-)

- **HBeAg (+) patients**
  - Treat for 6 - 12 months after documented HBeAg seroconversion [HBeAg (-), HBeAb (+)]
  - OR
  - Treat until HBsAg (-)

Degertekin B, Lok AS. Ann Intern Med 2007;147:62-64
The ABC’s of HBV Therapy

A. Stage the disease
B. Select one of the preferred drugs
C. Know when to stop

Controversies in HBV

Pregnancy
Immunosuppression
TWO QUESTIONS

1. Does the mother need treatment?
   - Elevated ALT + viremia = yes
   - Normal ALT, low viral load = no

2. Is the child at increased risk of infection?

Vertical HBV Transmission

- **Maternal viral load**
  - Single most important predictor for transmission
  - **High risk** = viral load > 200,000 IU (6 log copies)

- Other risk factors
  - Prolonged uterine contractions
  - Threatened pre-term labor
  - Prior child with HBV despite immune prophylaxis

Is Reducing Viral Load Effective?

- eAg (+) >6 log HBV-DNA pregnant subjects
- Telbivudine 600mg (n=53) vs. no anti-viral therapy (n=35)
  - Start therapy at 2nd or 3rd trimester
- All infants received HBIG and HBV vaccine
- Risk of HBsAg (+) child at 28 weeks:
  - Telbivudine: 0%
  - No antiviral therapy: 8.6%
- No safety issues noted


Safety of Therapy During Pregnancy

- None of the antiviral drugs are approved for use in pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Class</th>
<th>Human Pregnancy Experience (Registries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>C</td>
<td>&gt;10,000 (safe)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>B</td>
<td>&gt; 1,700 (safe)</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>B</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Entecavir</td>
<td>C</td>
<td>Very limited</td>
</tr>
</tbody>
</table>

Class A: Proven safe in well controlled studies
Class B: Safe in animal reproduction studies, no human studies
Class C: Adverse effect on the fetus in animal studies, no human studies; use if benefits outweigh risks

**HBV in Pregnancy**

### Recommended Approach

- Measure HBV-DNA at time of diagnosis and at the beginning of 3rd trimester

  - **>200,000 IU = High Risk**
  - **<200,000 IU = Low Risk**

- Consider tenofovir, telbivudine or lamivudine in the 3rd trimester

- All children receive HBlg and vaccine within 12 hours of birth

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**SHARED, INFORMED DECISION**

- No large randomized studies
- No long-term safety studies
- No clinical guidelines
  - Expert recommendations

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Involve all parties in the decision process!
Immune Suppression and HBV

- The immune system determines the activity of HBV
  - **Strong immune system:**
    - HBV controlled
  - **Impaired immune system:**
    - Uncontrolled viral replication
  - **Restoration of immune response**
    - Acute liver injury to clear HBV

Risk for HBV Reactivation

- **Chemotherapy**
  - Rituximab
- **Anti-TNF biologics**
- **Immunomodulators**
  - Azathioprine
  - Methotrexate
- **Long-term corticosteroid use**
- **Others**

References:
Recommendations

1. **Screen prior to immune suppression**
   - HBsAg, HBeAb (total)
   - If positive for either, measure HBV-DNA

2. **HBsAg or HBV-DNA positive:**
   - Start antiviral therapy
     - 2 weeks before and at least for 6-12 months after

3. **HBsAg (-), HBV-DNA (-), HBeAb (+)**
   - Start antiviral therapy\(^1\) **OR**
   - Monitor HBV-DNA periodically during immune suppression\(^2\)

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Take Home Points

1. Stage the disease, assess need for therapy
2. Choose appropriate therapy
3. Understand treatment endpoints
4. HBV + Pregnancy: Assess risk to mother and child
5. Immunosuppression – Always screen for HBV

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