Conflicts of Interest

• The Liver Disease and Hepatitis Program of the Alaska Native Tribal Health Consortium has received funding <$10,000 from Gilead in 2011
Goals of Presentation

• Understand natural history of chronic HBV infection
• Discuss management of HBV including role of HBV DNA testing, fibrosis markers, transient elastography and HBsAg levels
• Discuss antiviral agents used in adults
• Discuss HIV/HBV co-infection
• Discuss exacerbation of HBV associated with chemo and immunosuppressive therapy
Geographic Distribution of Chronic HBV Infection

HBsAg Prevalence
- □ 8% - High
- 2-7% - Intermediate
- <2% - Low
Natural History of Chronic HBV Infection

- Chronic HBV infection has a complicated course.
- Patients can go from state of high viral load and no liver disease to one of active liver disease followed by inactive disease then revert back to active liver disease again.
- Progression to advanced fibrosis can be rapid, slow or constant.
- During the inactive periods fibrosis and even early cirrhosis can be reversed over time.
- Bottom line: it’s hard to predict what will happen to an individual with chronic HBV infection.
Chronic HBV Viral Infection

• Chronic hepatitis B cannot be “cured”
• Integration of HBV DNA occurs into the human hepatocyte DNA over time
• A favorable outcome is suppression of hepatitis B virus DNA (HBV DNA) which can occur:
  - Naturally in many individuals as part of the natural history of this viral infection
  - Via antiviral therapy; which may have to be used long-term for an indefinite period of time
Long-Term Outcome of Chronic Hepatitis B Infection: Lifetime Risks

- Hepatocellular carcinoma (HCC)
  - 25%-40% of males
  - 10-15% females
- Cirrhosis
  - 10% to 20% of males and females
- Can we prevent carriers from getting HCC and/or cirrhosis?
- Can we detect HCC early when treatable?

Mathematical Model: Age-specific hepatitis B-related cirrhosis and HCC mortality

Goldstein Int J Epidemiol 2005;34;1329-39
CHRONIC HEPATITIS B: Definitions: NIH Workshop

- HBsAg-positive for at least 6 months
- Phases of Chronic hepatitis B
  - Immune Tolerant Phase: HBeAg+, normal ALT, HBV DNA > 200,000 IU/ml (>1 million copies)
  - Immune Active or Clearance Phase: elevated ALT, HBV DNA > 2,000 IU/ml, HBeAg or anti-HBe
  - Inactive Hepatitis B carrier: anti-HBe, ALT WNL, HBV DNA < 2,000 IU/ml
    - Reactivation of hepatitis
    - Clearance of HBsAg (“Recovered Phase”)

Hoofnagle, Hepatology 2007;45:1056-1075
## Phases of Chronic HBV

<table>
<thead>
<tr>
<th>Phase</th>
<th>HBeAg</th>
<th>HBV DNA</th>
<th>ALT</th>
<th>Liver Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune Tolerant</td>
<td>Positive</td>
<td>Very high &gt;200,000 IU/ml</td>
<td>Normal</td>
<td>No/mild inflammation/Fibrosis</td>
</tr>
<tr>
<td>Immune Active</td>
<td>Positive or Negative</td>
<td>&gt;2,000 IU/ml Usually &gt;20,000</td>
<td>Elevated</td>
<td>Inflammation and Fibrosis; Degree Varies</td>
</tr>
<tr>
<td>Inactive</td>
<td>Negative</td>
<td>&lt;2,000 IU/ml</td>
<td>Normal</td>
<td>Normal or mild</td>
</tr>
</tbody>
</table>
Suspect HBV infection? Use this algorithm to screen and intervene

**Screening at-risk patients**

- An individual in your care is at possible risk for HBV infection. (See note A.) You order tests for serum HBsAg and anti-HBs. Is the patient HBsAg+?
  - No -> Is the patient anti-HBs+?
    - Yes: The patient is immune to HBV; no follow-up is needed.
    - No: Vaccinate as appropriate, per patient’s risk factors.
  - Yes: If the patient is reported to have HB core antibody, it could indicate chronic infection, recovery from old infection, or a false-positive result. Confer with a specialist.

**Evaluating and monitoring HBsAg+ patients**

- You collect baseline data for levels of ALT, HBeAg, anti-HBe, and HBV DNA. (See note B.) Is the patient HBeAg+?
  - Yes: The patient is HBeAg– and anti-HBe+.
    - Is ALT level elevated, with HBV DNA >2000 IU/mL?
      - Yes: Patient is in the inactive phase. Retest HBeAg, HBV DNA, and ALT every 6 months. (See note C.)
      - No: Consult a specialist for advice on liver biopsy and treatment options. (See note D.)
    - No: Is ALT level normal, with HBV DNA >20,000 IU/mL?
      - Yes: Patient is in the immune tolerant phase. Retest HBeAg, HBV DNA, and ALT every 6 months. (See note C.)
      - No: If ALT level is elevated to ≥19 IU/L (woman) or ≥30 IU/L (man), the patient is in the immune active phase.

ALT, alanine aminotransferase; anti-HBe, antibody to HBeAg; anti-HBs, antibody to HBsAg; AST, aspartate aminotransferase; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e-antigen (protein produced by HBV, indicating heightened viral activity); HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma.

Source: Primary Care Provider Workshop on Hepatitis B, sponsored by the Hepatitis B Foundation in Doylestown, Pa (March 10-11, 2010).
Factors Associated with Progression of Chronic HBV

• Demographic:
  – Male Sex
    • Increase incidence HCC in males (1a)
  – Age
    • Increasing incidence of HCC with age (1a)
  – Family history (1b)

• Environmental and Social
  – Alcohol: Increase risk for HCC and cirrhosis (2c)
  – Aflatoxin exposure: increase risk of HCC (2c)
  – Tobacco: Increased risk for HCC (2c)
  – NAFLD: limited conflicting data (3)
Factors Associated with Progression of Chronic HBV: Viral

- Genotype
- Other viral co-infections:
  - HIV:
    - Increase HBV DNA levels
    - Increased risk of cirrhosis/HCC
    - Increased risk of opportunistic and AIDS related events and overall death rate
  - HDV: Increase risk of cirrhosis
  - HCV: HCV usually dominant but Increase risk of HCC
- High HBV DNA level over time (>5 log copies or 20,000 IU/ml) in persons > 40 years (REVEAL Study Taiwan)
AIDS or Death Events by HBV Serologic Status

Logrank = 20.29  P < .001

<table>
<thead>
<tr>
<th>Years From Seroconversion</th>
<th>Chronic HB</th>
<th>Isolated HBcAb</th>
<th>Resolved HB</th>
<th>HB Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>64</td>
<td>82</td>
<td>474</td>
<td>1732</td>
</tr>
<tr>
<td>1</td>
<td>63</td>
<td>81</td>
<td>452</td>
<td>1622</td>
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<td>2</td>
<td>60</td>
<td>76</td>
<td>433</td>
<td>1414</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>69</td>
<td>405</td>
<td>1240</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>62</td>
<td>365</td>
<td>1082</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>55</td>
<td>330</td>
<td>940</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>47</td>
<td>280</td>
<td>812</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>40</td>
<td>241</td>
<td>682</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>31</td>
<td>205</td>
<td>569</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>23</td>
<td>117</td>
<td>468</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>21</td>
<td>153</td>
<td>405</td>
</tr>
</tbody>
</table>
Other Tests Commercially Available

• Pre-core mutant
  – Stop Codon mutation: Prevents production of HBeAg
  – Presence may mask high levels of HBV DNA but often found in persons with low levels
  – Some studies show increase risk of cirrhosis
  – REVEAL study showed presence was a good prognostic factor
  – My advice: Don’t waste your money
Basal Core Promoter (BCP)

- Associated with increase risk of HCC and cirrhosis in cross sectional studies
- In REVEAL study, associated independently with increased risk of HCC
  - (BCP vs. no BCP (1149 vs. 359/100,00)
  - Along with viral load, genotype C and absence of PC mutant (2254/100,000)
- More prospective and cost effective studies to determine how to use BCP as a prognostic marker especially in non B/C genotypes

Yang JNCI 2008;100:1134-1143
HBV Genotypes

- 8 Genotypes identified: A-H
- Based on $\geq 8\%$ divergence of HBV complete sequence
- Sub-genotypes: Differ in complete genomic sequence by between 4\% and 8\%
- Disease outcome appears to be strongly associated with HBV genotype

McMahon Hepatology International; 2009;3:334-42
Fig. 2 Geographic Distribution of HBV Genotypes and Sub-Genotypes
HBV Genotypes and Disease Outcome

• Increased incidence of complications
  – Genotype C: Prolonged period of HBeAg positivity, HCC and Cirrhosis starting age 40
  – Genotype B2-6: HCC & cirrhosis lower than C but higher than other HBV genotypes
  – Genotype F: High incidence of HCC in children

• Decreased incidence of complications
  – Genotypes B1 and B6
Median Age of HBeAg Seroconversion by Genotype: Median 21 Years Follow-up*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. HBeAg+</th>
<th>Age 50% lost HBeAg</th>
<th>Age 75% lost HBeAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₂</td>
<td>34</td>
<td>19.8</td>
<td>32.1</td>
</tr>
<tr>
<td>B₆</td>
<td>6</td>
<td>19.5</td>
<td>27.5</td>
</tr>
<tr>
<td>C₂</td>
<td>36</td>
<td>47.8</td>
<td>58.1</td>
</tr>
<tr>
<td>D</td>
<td>305</td>
<td>18.0</td>
<td>27.3</td>
</tr>
<tr>
<td>F₁</td>
<td>126</td>
<td>16.1</td>
<td>24.5</td>
</tr>
</tbody>
</table>

Gastroenterology 2007;133:1452-57  *P<.001 genotype C vs. other genotypes
Reversions from anti-HBe back to HBeAg: Median 21 Years Follow-up*

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Reversions back to HBeAg No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A₂</td>
<td>3/32 (9%)</td>
</tr>
<tr>
<td>B₆</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>C₂</td>
<td>8/22 (36%)</td>
</tr>
<tr>
<td>D</td>
<td>42/284 (15%)</td>
</tr>
<tr>
<td>F₁</td>
<td>49/122 (40.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>102/466 (22%)</td>
</tr>
</tbody>
</table>

*p<.001 genotypes C and F compared to all others

Gastroenterology 2007;133:1452-57
Other Tests:

- **HBsAg levels**
  - Immune tolerant > immune active > inactive
  - If < 1,000 and HBV DNA < 2,000 IU/ml predict remaining in inactive phase*
  - Rapid drop may predict impending HBsAg loss

- **Serologic markers**
  - Good at predicting no or very mild fibrosis or severe fibrosis
  - No better than flip of the coin for those ~2/3rds of patients who fall in the middle of the scoring range

- **Transient Elastography for liver stiffness:** fewer studies but comparable to HCV for advanced fibrosis
  - Acute or exacerbation of HBV, increasing BMI and operator experience of < 500 exams may give unreliable results^

* Brunetto Gastroenterology 2010;139:483-90
Treatment of Chronic Hepatitis B

• What is the evidence that treatment improves outcome?
• Who should be treated?
• When should treatment be initiated?
• How long should antiviral treatment be given?
• How do we deal with antiviral resistance?
The impact of lamivudine on the risk of progression

- 651 cirrhosis patients with evidence of viral replication

Patients with disease progression (%)

<table>
<thead>
<tr>
<th>Time to disease progression (months)</th>
<th>Placebo (n=215)</th>
<th>Lamivudine (n=436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>6</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>12</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td>18</td>
<td>20%</td>
<td>19%</td>
</tr>
<tr>
<td>24</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>30</td>
<td>27%</td>
<td>26%</td>
</tr>
<tr>
<td>36</td>
<td>30%</td>
<td>29%</td>
</tr>
</tbody>
</table>

p=0.001 ITT population

- Benefit reduced with YMDD emergence

Long-Term Goals of Antiviral Therapy

- Decrease risk of development of cirrhosis
- If cirrhosis is present, decrease risk of decompensation
- If decompensated cirrhosis present, treat to revert patient to compensated cirrhosis
- Decrease risk of development of hepatocellular carcinoma
AASLD Practice Guidelines: Chronic HBV

- Routine, periodic follow-up of all carriers should be performed by a health care provider (MD or RN)
- Follow-up interval of every 3-12 months depending on circumstances

Lok & McMahon. Hepatology 2009
Goals of therapy: HBeAg-Positive

- HBeAg-positive
  - Best response of ALT > 2 times upper limit of norm (80 U/L)
  - HBeAg loss and seroconversion to anti-HBe
  - durable suppression of HBV DNA to low or undetectable levels
  - normalization of ALT
  - durability of HBeAg seroconversion ≈70–90%
Goals of therapy: HBeAg-Negative

- HBeAg-negative
  - Treat persons with at least moderate hepatitis or fibrosis (Ishak, Metavir stage 2/4)
  - HBeAg seroconversion not an endpoint
  - durable suppression of HBV DNA to low or undetectable levels
  - normalization of ALT
  - long-term therapy the rule with oral agents
New Goals for Evaluation of Treatment of Patients: 2009

- Elevated ALT or AST and HBV DNA > 2,000 IU/ml
- HBV DNA > 20,000 and ALT > 20 women or 30 men in persons age 40 years or over
- Persons with persistently elevated ALT or AST levels but HBV DNA < 2,000 on all follow-up draws
  - Evaluate for other liver diseases
  - Follow ALT and HBV DNA to detect flares
Management of Chronic HBV Infection*

HBsAg +

HBeAg

Positive

ALT < 1 X ULN
- Q 6 mo ALT
- Q 12 mo HBeAg

ALT 1-2 X ULN
- Q 3 mo ALT
- Q 6 mo HBeAg
- Liver bx if persistent or age > 40, Rx as needed

ALT >2 X ULN
- Q 1-3 mo ALT, HBeAg
- If persistent, Liver bx & Rx;
  Immediate Rx if jaundice or decompensated

* HCC surveillance if indicated
Management of Chronic HBV Infection*

HBsAg +

HBeAg

Negative

ALT > 2X ULN
DNA > 20,000 IU/mL
Liver bx & Rx

ALT 1-2X ULN
DNA 2,000-20,000 IU/mL
Q 3 mo ALT & DNA
If results persist, liver bx, treat as needed

ALT < 1X ULN
DNA < 2,000 IU/mL
Q 3 mo ALT X 3,
Then Q 6-12 mo
If ALT still WNL

* HCC surveillance if indicated
Drugs for Treating Chronic HBV

• FDA approved:
  – α2 Interferon: Regular and Pegylated
  – Lamivudine
  – Adefovir Dipivoxil
  – Entecavir
  – Telbivudine
  – Tenofovir

• Available but not approved for HBV:
  – Emtricitabine (FTC)
  – Truvada (Tenofovir + Emtricitabine)
Which Drugs to Choose

• First line drugs
  – Peg-Interferon: Expensive, no resistance
  – Entecavir: Very potent, less resistance but don’t use in lamivudine experienced persons, expensive
  – Tenofovir: very potent, less expensive, resistance?

• Second line drugs
  – Lamivudine: Potent, high resistance rate, cheapest
  – Telbivudine: Potent, expensive, resistance common
  – Emtricitabine: Potent, expensive, resistance common
  – Adefovir: Less potent, Fails in 30%, expensive
HBeAg Seroconversion after Peg-Interferon in HBV: IL28 and HBV Genotype

Retrospective analysis of 205 patients from 11 European and Asian hospitals
Does HBV DNA genotype and/or IL28B genotype influence response to Peg-IFN?

<table>
<thead>
<tr>
<th>HBV Genotype</th>
<th>IL28</th>
<th>% HBeAg seroconversion</th>
<th>IL28</th>
<th>% HBeAg seroconversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2</td>
<td>CC</td>
<td>60%</td>
<td>CT/TT</td>
<td>38%</td>
</tr>
<tr>
<td>B</td>
<td>CC</td>
<td>58%</td>
<td>CT/TT</td>
<td>20%</td>
</tr>
<tr>
<td>C</td>
<td>CC</td>
<td>51%</td>
<td>CT/TT</td>
<td>33%</td>
</tr>
<tr>
<td>D</td>
<td>CC</td>
<td>7%</td>
<td>CT/TT</td>
<td>8%</td>
</tr>
</tbody>
</table>

Sonneveld et al. Gastroenterology 2012;142:513-20
How to Follow Patients on Nucleoside Analogues

• ALT, AST, HBV DNA every 3-6 months
• If HBV DNA level increases 1 log or above 2,000 units, test for resistance
Duration of Treatment

• HBeAg-positive:
  – Until at least 6 months after loss of HBeAg and appearance of anti-HBe

• HBeAg-negative (anti-HBe positive)
  – Interferon: 1 year
  – Nucleoside analogues: Indefinitely
Good News: Early Cirrhosis Can be Completely Reversed!

• Remove the cause of cirrhosis and reversal will take place over about 10 years
  – HBV: Antiviral medication (tenofovir)
  – HCV: Treat and cure
  – Alcohol: Stop drinking alcohol

• Even 30% to 50% of persons with decompensated cirrhosis will become compensated (look normal clinically and by LFT) after proper treatment
Liver Fibrosis Regressed Significantly over 5 Years of Treatment with TDF*

- Patients with cirrhosis (Ishak score ≥5): 28% at Baseline, 8% at Year 5

Afdhal N et al. EASL 2012, Poster 497
74% of Patients with Cirrhosis at Baseline Had No Histologic Evidence of Cirrhosis at Year 5

- 74% (71/96) had no histologic evidence of cirrhosis (Ishak score <5) at Year 5
- 1% (3/252) of non-cirrhotics (Ishak score ≤4) progressed to cirrhosis at Year 5 (P <0.001; McNemar’s test)

Change in Ishak Scores at Year 5 for Patients with Cirrhosis at Baseline

73% of patients had ≥2 unit reduction

Afdhal N et al. EASL 2012, Poster 497
HBV/HIV Co-Infection Continued

• No increased risk of hepatotoxicity due to HAART in co-infected persons
• High level of HBV DNA at initiation of HAART associated with higher baseline ALT level and increase risk of ALT flares during therapy
  – Increased risk of hepatotoxicity is due to co-presence of HBV
• High probability of resistance to 3TC occurs
• Recent reports of persons on HAART developing liver decompensation or HCC who have non detected levels of HIV RNA
Failure to Treat HBV in HIV Infected Patients: Consequences

- Rapid development of 3TC resistance to HBV
- Flares of hepatitis with resistance or immune reconstitution which may be misinterpreted as hepatotoxicity to ART
- Long-term consequences of ignoring HBV may take 1 or more decades to occur:
  - Increase in HCC and liver decompensation
  - In patients whose HIV is under good control, increased risk of AIDS related events and death
AIDS or Death Events by HBV Serologic Status

Logrank = 20.29 P < .001

Chun JID 2012;205:185-93
Treatment of HBV/HIV Co-Infection

- Treatment of both infections
  - Tenofovir plus emtricitabine (Truvada®) or
  - Tenofovir plus 3TC
- Treatment of HBV or HIV only: now considered a no-no. All co-infected patients should be put on TDF based therapy
Exacerbation of Hepatitis B during/after Chemo or Immunosuppressive Therapy

• Summary of 14 studies revealed that 33% of patients who are HBsAg+ will have a flare of hepatitis after therapy
  – 13% had liver failure
  – 5.4% expired due to liver failure
  – Highest risk with lymphoma
• Can also occur with TNF inhibitors
• Lamivudine prophylaxis reduced risk of reactivation from 79% to 100%
  – No patients died or developed liver failure

Recent Position Paper by AASLD and CDC

- Paper to refute American Society of Oncology who were unenthusiastic
- Recommended
  - Screen all persons on cancer chemotherapy or immunosuppressive therapy for at least HBsAg
  - Consider screening those on intensive therapy with Rituximab or for leukemia/lymphoma for anti-HBc
  - Antiviral prophylaxis for all those HBsAg+
  - More research needed

Lok et al. Ann Intern 2012;156:743-45
Alaska Native Liver Disease Approach

- Pre chemo or immunosuppressive therapy
  - HBsAg-positive:
    - HBV DNA >2,000: Tenofovir or Entecavir: possible long-term duration of treatment
    - HBV DNA <2,000: Lamivudine and stop therapy 6-12 months post chemo/immuno therapy
  - Anti-HBc+/HBsAg-negative and on potent chemotherapy/immunosuppression
    - HBV DNA absent: follow HBV DNA q 3 months on therapy; treat as above if HBV DNA is positive or becomes positive
Conclusions

- Persons with chronic HBV infection need lifelong follow-up
- Patients with moderate or advanced fibrosis or inflammation can benefit by treatment
- Patients undergoing chemo or immunosuppressive therapy need HBV serology testing
- Perform surveillance of HBV infected persons for HCC as per AASLD guidelines