Hepatitis B – Epidemiology and Screening Populations at Risk

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• Overview of treatment
• Diagnostic markers
• Modes of transmission
• Natural history of infection
• Screening policies in the United States
• Global patterns of endemicity
• Global patterns of transmission
• Vaccination recommendations for travelers

Hepatitis B

• 350 Million people chronically infected worldwide
  – HBV vaccination programs will decrease future global burden and evidence of reduced burden is mounting in country-specific populations.
  – Vaccination programs have still not been implemented in ALL countries maintaining reservoirs of infection
• 1.25 million carriers in the United States
• 5-10% liver transplants
• 75% all HCC
Hepatitis B Remains a WORK-IN-PROGRESS

- Controversy regarding who should be treated
- Seven Current Treatments Available
  -- Recommendations based on comparisons with lamivudine and adefovir
- Goal of therapy is based on "surrogate endpoints"
  -- Prevent the development of progressive liver disease
  -- No RCT that connect ALT, HBV DNA, liver histology to disease progression
  -- DESPITE THIS PERSISTANCE OF DNA APPEARS TO BE ASSOCIATED WITH DISEASE PROGRESSION AND HCC

### Candidates for therapy

<table>
<thead>
<tr>
<th>NIH Consensus</th>
<th>AASLD</th>
<th>EASL</th>
<th>Kehrle EB, et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT normal, HBe Ag (+), HBV DNA &lt; 20,000</strong></td>
<td>No comments</td>
<td>Do not treat (monitor)</td>
<td>No comments</td>
</tr>
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<td><strong>ALT normal, HBe Ag (+), HBV DNA ≥ 20,000</strong></td>
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<tr>
<td><strong>ALT ≤ 2×ULN, HBe Ag (-), HBV DNA &lt; 20,000</strong></td>
<td>No comments</td>
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<tr>
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<td>No comments</td>
<td>Do not treat (monitor)</td>
<td>No comments</td>
</tr>
<tr>
<td><strong>Cirrhosis, HBV DNA &lt; 2,000</strong></td>
<td>Treat</td>
<td>Treat if ALT elevated</td>
<td>Treat</td>
</tr>
<tr>
<td><strong>Cirrhosis, HBV DNA ≥ 2,000</strong></td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td><strong>Decompensated, HBV DNA DETECTABLE</strong></td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
</tbody>
</table>

- Interferon alfa-2b
- Pegylated interferon alfa-2a
- Lamivudine
- Adefovir
- Entecavir
- Telbivudine
- Tenofovir
Hepatitis B Remains a WORK-IN-PROGRESS

- Controversy regarding who should be treated
- Seven Current Treatments Available
  - Recommendations based on comparisons with lamivudine and adefovir
- Goal of therapy is based on “surrogate endpoints”
- Questions remain -
  - Which groups of patients will benefit?
  - What point in the course of the disease should therapy be started?

Antiviral Treatment

- Reduction (elimination) of risk of cirrhosis
- Reduction of HCC risk
- Unknown safety of long-term treatment
- Possibility of antiviral resistance
- Cost

Glossary of Hepatitis B Diagnostic Markers

- **HBsAg** (Hepatitis B surface antigen)
  - Makes up viral envelope. Cellular and humoral immunity. Basis for vaccines. Marker for hepatitis B infection. A small number of chronic carriers will lose HBsAg over time.
- **HBsAg** (Hepatitis B core antigen)
  - Not commonly found in circulation
  - Marker of viral replication
- **HBV DNA** (Nucleic acid testing)
  - The best indication of active viral replication
- **HBeAb** (Anti-HBe to HBsAg)
  - Generally confers protective immunity
- **HBeAb** (Antibody to HBsAg)
  - Detectable in virtually ALL patients exposed to hepatitis B. Presence does not distinguish acute from chronic infection
- **HBeAb** (Anti-HBe to HBsAg)
  - Appears once e-antigen is cleared
Modes of Transmission

• Incubation 45 – 160 days
• Remains viable on environmental surfaces for \( \geq 7 \) days.
• Percutaneous and mucous membrane exposure to blood and body fluids*

*Although HBsAg detected in a wide variety of body fluids only blood, semen and saliva have been demonstrated to be infectious

Modes of Transmission

• Percutaneous exposures
  – Transfusion of blood or blood products
  – Contaminated equipment used for injections and other invasive medical procedures
  – Illicit injection drug use
  – Tattoos, acupuncture

Modes of Transmission

• Mucous Membrane Exposure
  – Sexual transmission from mucous membranes being exposed to blood or serum-derived body fluids
  – Perinatal transmission – children born to women who are e-antigen positive have a 70 - 90% chance of infection at 6 months, 10 – 40% in infants born of e-antigen negative mothers.
Modes of Transmission

- **Vertical Transmission**
  - Mother to child
  - Generation to generation through close contact and sanitary habits
- **Early life horizontal transmission**
  - Bites, lesions, sanitary habits
- **Adult horizontal transmission**
  - Sexual contact, injection drug use, medical procedure exposure

Natural History of Hepatitis B

Mother-to-child transmission

Child-to-child transmission

Immune-tolerant phase

Immune-active phase

Inactive carrier phase

HBeAg Negative CHB

Cirrhosis

Hepatocellular carcinoma

Screening for HBV

- High-risk groups
  - Household and sexual contacts
  - History of IDU
  - History of STD
  - MSM
  - Inmates
  - Chronically elevated aminotransferase levels
  - Individuals infected with HCV or HIV
  - Renal dialysis patients
  - Pregnant women*

Adapted from Keefe EB, et al., Clinical Gastroenterology and Hepatology 2008;12:1315-1341
Endemicity of Infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Infection</td>
<td>0.10 – 1%</td>
<td>2 – 7%</td>
<td>8 – 15%</td>
</tr>
<tr>
<td>Past Infection Prevalence</td>
<td>4 – 15%</td>
<td>16 – 55%</td>
<td>40 – 90%</td>
</tr>
<tr>
<td>Perinatal Infection</td>
<td>Rare (&lt; 10%)</td>
<td>Uncommon (10 – 60%)</td>
<td>Common (&gt;20%)</td>
</tr>
<tr>
<td>Early Childhood Infection</td>
<td>Rare (&lt; 10%)</td>
<td>Uncommon (10 – 60%)</td>
<td>Common (&gt;20%)</td>
</tr>
<tr>
<td>Adolescent/Adult Infection</td>
<td>Very Common (70 – 90%)</td>
<td>Common (20 – 50%)</td>
<td>Uncommon (10 – 20%)</td>
</tr>
</tbody>
</table>

Global Patterns Of Transmission
- Approximately 60% of the world’s population lives in highly endemic areas

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>1.3 billion</td>
</tr>
<tr>
<td>Indonesia</td>
<td>222 million</td>
</tr>
<tr>
<td>Nigeria</td>
<td>132 million</td>
</tr>
</tbody>
</table>

- Southern Europe, the Middle East and South Asia have intermediate endemicity
- Most of Central and South America have low endemicity – western Amazon Basin

Measurement Issues
- Data from studies conducted at different times may produce misleading disease prevalence because of different testing techniques
- Vaccination produces a serologic response that can be confused with infection prevalence when only anti HBs is used.
- Diversity within areas or countries
• Southeast Asia: all countries
• Africa: all countries
• Western Pacific, South Pacific Islands: all countries
• Middle East: except Cyprus and Israel
• European Mediterranean: Malta and Spain
• Eastern Europe: all countries except Hungary
• The Arctic (indigenous populations of Alaska, Canada, and Greenland)
• South America: Ecuador, Guyana, Suriname, Venezuela, and Amazon regions of Bolivia, Brazil, Colombia, and Peru
• Caribbean: Antigua and Barbuda, Dominica, Grenada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, and Turks and Caicos
• Central America: Guatemala and Honduras
• Southeast Asia
  - Extends from India to Indonesia
  - 1997 WHO estimated HBsAg seroprevalence between 1% and 10% - Total carriers as high as 130 million
  - Thailand = 6%
    - Mostly > Females
    - Healthcare workers
    - Sexual activity
    - Lower socioeconomic levels
  - India = 4%
    - Variability - increasing prevalence from north to south
    - Early life horizontal transmission and mode of transmission
    - Younger ages
    - Non-sterile medical equipment
    - Blood Transfusion
• **Africa**
  - WHO African region includes all of sub-Saharan Africa and Algeria = between 5% and 19%
  - After Asia – Africa has the highest number of carriers with as many as 12.5 million premature deaths due to HBV.
    - Western Africa with historical HBsAg seroprevalence in Gambia and Senegal > 10%
    - Probably lower now due to implementation of vaccination programs
    - Early life horizontal most predominant mode of transmission but vertical and adult horizontal account for transmission as well.

• **Africa**
  - Gambia – first country in Africa to institute mass infant immunization (but not universally included)
  - However both Gambia and Senegal report reduced HBV burden (10 to 0.6% and 18.7 to 2.2%)
  - In contrast to Asia HBV in newborns less common in Africa. Early life horizontal accounts for the majority of infection endemcity.
* Western Pacific, South Pacific Islands
  - 1987 WHO estimated HBsAg seroprevalence between 2% and 31% - Total carriers as high as 150 million
  - Highest level of endemic HBV in the world
  - Low prevalence in Japan but extremely high in small South Pacific Island nations
    - China, South Korea, Taiwan = 10-12%
      - Vertical
      - Early life horizontal
      - Declining HBsAg prevalence after 65 years*

* Due to clearance or increased death rate?

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  - Highest level of endemic HBV in the world
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    - China, South Korea, Taiwan = 10-12%
      - Vertical
      - Early life horizontal
      - Declining HBsAg prevalence after 65 years
    - Philippines = 10% (5% - 10%) *
    - Adult horizontal
      - Sexual contact
      - IV drug use
      - Nonsterile medical equipment

* Western Pacific, South Pacific Islands
  - As a result of vaccination programs, many countries in Asia that once had high endemicity are now of intermediate endemicity.
  - Mainland China is now the only Western Pacific country with endemicity > 8%
Europe
- Extends from Iceland to Turkey and includes Israel including countries that comprise the former Soviet Union
- Estimated HBsAg seroprevalence in this region between 0.3% and 12% with up to 3.5 million carriers
- Overall region considered to be intermediate in endemicity but wide variation
  - Northern European Countries – Low prevalence
  - Southerly Mediterranean countries – Intermediate prevalence
    - Western Europe incidence – 6/100,000 in south to 1/100,000 in north
    - Central Europe incidence – 20/100,000 to 100/100,000 in eastern Asian Countries
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    • Northern European Countries – Low prevalence
    • Southerly Mediterranean countries – Intermediate prevalence
      – Risk factors include heterosexual activity and MSM, IVDU, perinatal exposure and household contact
      – Central and Eastern Europe – nosocomial transmission via blood products and medical procedures

• Europe
  – Extends from Iceland to Turkey and includes Israel including countries that comprise the former Soviet Union
  – Estimated HBsAg seroprevalence in this region between 0.3% and 12% with up to 3.5 million carriers
  – Overall region considered to be intermediate in endemicity but wide variation
    • Northern European Countries – Low prevalence
    • Southerly Mediterranean countries – Intermediate prevalence
      – Central and eastern Europe – culturally and geographically diverse
      – Vaccination has been implemented – but varies
• North America
  – Overall – low level of Hepatitis B
  – 0.2 – 0.5% in United States
  – Native Alaskan population – high prevalence
  – Similarly prevalence is low in Canada but higher in Native Canadians
    • Routes of transmission – adult horizontal although vertical routes observed in immigrants from areas of high endemicity and Native populations near the Arctic Circle.

• South and Central America
  – Area includes Central and South America and Mexico and Islands of the Caribbean region
  – Hepatitis Bs Antigen seroprevalence between 0.5% and 3%
  – Total number of carriers ~ 11 million
    • Highest in western Amazon basin, including parts of Brazil, Colombia, Peru and Venezuela (~ 8%)
    • Lowest in Chile, Uruguay, and Argentina.
    • In Brazil, Colombia, Panama, Peru and Venezuela prevalence is highest in native populations.
    • Approximately 3% in Haiti, Dominican Republic and Honduras
Hepatitis B Vaccine Recommendations

• In 1992 WHO recommend the integration of hepatitis B vaccine into the national immunization programs of highly endemic countries by 1995 and ALL other countries by 1997.
• As of 2004 more than 150 (78%) of 192 WHO member nations had adapted universal childhood vaccination policies.
• Notably absent were several highly endemic countries – most in sub-Saharan Africa

Hepatitis B Vaccine Recommendations

• Several highly developed countries with low endemicity including the UK, Japan and the Scandinavian countries do not routinely vaccinate but target at-risk populations.

Vaccination Policies for Travelers

• Currently the vaccination recommendation for travelers to areas of high and intermediate endemicity is unclear and there are few existing data with which to set policy.
• CDC Recommendations
  "...There are no data with which to assess the risk for HBV infection among US travelers. Published case reports of travelers acquiring hepatitis B during travel are rare. The risk for HBV infection among international travelers is low. However, the risk of HBV infection is considered higher in countries where the prevalence of chronic HBV infection is intermediate or high. Expatriates, missionaries, and long-term aid workers may be at increased risk for HBV infection..."
• CDC Recommendations (continued)
  "...Hepatitis B vaccination should be administered to all unvaccinated people traveling to areas with intermediate or high prevalence of chronic hepatitis B (hepatitis B surface antigen prevalence ≥2%)..."

• Netherlands
  – Dutch national HBV travelers' guidelines advise HBV vaccinations for ALL persons traveling to endemic countries for > 3 months or for persons with other risk factors (sex tourists, people involved in dangerous sports, frequent travel)
  – More recent studies in the Netherlands based on questionnaires have found risky behaviors such as accidents, dental or medical treatment, tattooing, sports activities and sexual contact suggest that 33%-76% of these travelers to endemic countries were at risk.

  Sonder GJB, et al., Journal of Travel Medicine 2009

• Netherlands
  – In a retrospective analysis all acute HBV cases in Amsterdam between 1992 and 2003 to determine what proportion of acute HBV infections were travel related and imported from endemic countries.

  Sonder GJB, et al., Journal of Travel Medicine 2009
Vaccination Policies for Travelers

• Netherlands
  – Findings of an earlier prospective study that the HBV risk for short-term tourists endemic countries was very low (17 cases in 12 years during which an estimated 13 million people had traveled to endemic areas)
  – Long-term travelers from low-endemic origin were more likely to have sex with local population.
  – The HBV risk for immigrants from endemic countries who VFR, however, was higher. This seemed to be the case irrespective of duration of visit.
  – Recommendation was to include all immigrants in the risk group vaccination campaign.

Sonder GJB, et al., Journal of Travel Medicine 2009

5. Shepard CW, et al., Epidemiologic Reviews 2006; 28: 112-125