Lecture 10  Hepatitis B
Hussaini

**EPIDEMIOLOGY:**
- Approx. one third of the global population has been exposed to HBV
  - 350-400 million individuals harbor chronic HBV
  - 1 million people die every year due to the consequences of CHB
  - Cirrhosis, HCC (hepatocellular carcinoma)

**MODE OF TRANSMISSION:** contact with blood or bodily fluids
- Perinatal (as high as 90% in HBeAg+ mothers)
- Sexual transmission
- Percutaneous inoculation
  - Needlestick or sharing needles (IVDU)
  - Contaminated tattoo or piercing equipment
- Transfusions
- Close person-to-person contact (RARE)
  - Bites, cuts, toothbrush or razor sharing
  - Breast feeding

**MODE OF TRANSMISSION OF HBV & CHRONICITY:**
- HORIZONTAL (person → person) = LOW RISK OF CHRONICITY
  - Adults and children > 5 years = 2% CHB
  - 1-5 years old = 30% CHB
- VERTICAL (mother → newborn) = HIGH RISK OF CHRONICITY
  - > 90% of infected infants progress to CHB

**HBV NATURAL HISTORY & COMPLICATIONS:**

**HEPATITIS B VIRAL PROTEINS:**

- **HBsAG**
  - Hepatitis B surface antigen
  - Envelope protein
  - Marker of HBV infection
  - Antibodies against HBsAg signify recovery
  - Persistence of HBsAg for > 6 months represents CHB

- **HBeAG**
  - Hepatitis B e antigen
  - Soluble nucleocapsid protein
  - Serum marker of active viral replication
  - Accompanied by high serum HBV DNA (>100,000 – 1 million IU/mL)

- **HBcAG**
  - Hepatitis B core antigen
  - Structural nucleocapsid core protein
  - Anti-Hbc + signals past exposure

**CLINICAL PHASES OF CHB:**

**INTERPRETATION OF HBV SEROLOGIC PANEL:**

<table>
<thead>
<tr>
<th>TESTS</th>
<th>RESULTS</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbsAg</td>
<td>Negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Anti-Hbc</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HbsAg</td>
<td>Negative</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>Anti-Hbc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>HbsAg</td>
<td>Negative</td>
<td>Immune due to hepatitis B vaccination</td>
</tr>
<tr>
<td>Anti-Hbc</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HbsAg</td>
<td>Positive</td>
<td>Acutely infected</td>
</tr>
<tr>
<td>Anti-Hbc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IgM anti-Hbc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Anti-Hbs</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>HbsAg</td>
<td>Positive</td>
<td>Chronically infected</td>
</tr>
<tr>
<td>Anti-Hbc</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>IgM anti-Hbc</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

**CURE AS A GOAL OF THERAPY:**
- ACTUAL CURE = very difficult (if not impossible)
  - True cure = all traces of HBV gone from liver (like HCV)
- FUNCTIONAL CURE = attainable!
  - Prevent progression to cirrhosis and ESLD
  - Prevent HCC development

**SURROGATE MARKERS FOR RESPONSE:**

**ASLD GUIDELINES: WHEN TO START HBV THERAPY**

<table>
<thead>
<tr>
<th>HBsAg positive</th>
<th>HBsAg negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV DNA (IU/mL)</td>
<td>ALT</td>
</tr>
<tr>
<td>&gt; 20,000</td>
<td>≥ 2 x ULN</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**TREATMENT ALTERNATIVES:**

**TREATMENT DURATION:**

- Peginterferon Alfa-2A: 48 weeks
- Nucleoside analogues: Treat until ALL:
  - HBV DNA undetectable
  - HBeAg seroconversion
  - 6-12 months of consolidation therapy
  - Sustained response in 50-90%

- Peginterferon Alfa-2B: 180 mcg SC weekly
  -選取

- Entecavir (ETV): 0.5 mg PO daily
  - 1 mg if lamivudine resistance or decompansated cirrhosis
  - < 50
  - High potency, high genetic barrier to resistance
  - 無

- Tenofovir Alafenamide (TAF): 25 mg PO daily
  - < 50
  - Recommended

- Tenofovir Disoproxil Fumarate (TDF): 300 mg PO daily
  - < 15
  - X

- Lamivudine (3TC, LAM): 100 mg PO daily
  - < 50
  - Low genetic barrier to resistance

- Efavirenz: 600 mg PO daily
  - 1 mg if lamivudine resistance
  - < 50
  - Recommended

- Relapse frequent even if HBV DNA undetectable

**Comments**

- Select populations
- High potency, high genetic barrier to resistance
- Recommended
- Life-long therapy recommended

**Preferred**

- X
- V
- X
**PEG-INTERFERON ALPHA:**
- MOA: dual immunomodulatory and antiviral activity against HBV
- ↓ cirrhosis, HCC and liver-related death in long-term responders
- Consider in young women contemplating pregnancy, HBeAG +, genotype A and B, ↑ ALT
  - ADVANTAGES:
    - Fixed duration of treatment (typically 48 hrs)
    - Superior durable serologic response off treatment
    - 80-90% after 4-8 years
    - Greater rates of HBeAg seroconversion
    - ↑ HBsAg seroconversion
  - DISADVANTAGES:
    - +++ side effects
    - Moderate antiviral effect
    - Risk of decompensation in cirrhotics
    - SC injection

**LAMIVUDINE:**
- The first oral agent approved for hepatitis B
- High rate of drug resistance with longer duration of use
  - 65-70% after 4-5 years of therapy
- +++ landmark trials on clinical outcomes:
  - Slower disease progression and ↓ HCC
  - Benefit in patients with decompensated cirrhosis
  - Safe & effective in ↓ vertical transmission (+ HBIG & vaccine)

**ENTECAVIR:**
- A potent guanosine analogue that inhibits HBV DNA replication at 3 different steps
  - >100-fold more potent than either adefovir or lamivudine
- High genetic barrier for resistance in treatment-naïve
  - 1.2% risk of cumulative resistance in 5 years
- Resistance ↑ to 51% in 5 years in LAM refractory pts
- Less effective in lamivudine resistance
  - Increase dose to 1.0 mg once daily?

**TENOFORVIR DISOPROXIL FUMARATE (TDF):**
- An acyclic nucleotide analogue of adenosine
  - Structurally similar to Adefovir
- Potent in vivo and in vitro activity against both HIV and HBV
- No cross-resistance with lamivudine but there is with adefovir
- Viral breakthrough due to resistance is rare
- Durable HBV DNA suppression (up to 96-130 wks of therapy)
- ADRs: renal impairment (AKI, Fanconi’s syndrome), decreased BMD

**TENOFOVIR ALAFENAMIDE (TAF):**
- Improved pharmacokinetics (vs. TDF) = reduces systemic exposure to tenofovir and potentially improves renal and bone safety
  - 92% decrease in systemic exposure to tenofovir with TAF 25 mg vs. TDF 300 mg
- Phase 3 registration trials revealed:
  - TAF non-inferior to TDF in both HBeAg +ve and -ve patients
  - Less reduction in eGFR and BMD
- No dosage adjustments needed in pts with CrCl > 15 mL/min

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**Hepatitis B Reactivation:**

**Overview:**
- Clinical syndrome characterized by an abrupt, marked increase in HBV replication usually with elevations in ALT/AST and sometimes with jaundice
  - Loss of immune control over viral replication
- Occurs in pts with active (HBsAg+) and resolved (HBsAg-, anti-HBc+) HBV
- Can occur during treatment with many immunosuppressive agents
  - May occur up to 12 months after IMS treatment
  - Preventable by antiviral prophylaxis

**Definition of HBV Reactivation:**

<table>
<thead>
<tr>
<th>Virologic</th>
<th>Biochemical</th>
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<tbody>
<tr>
<td>100-fold (2 log) IU/mL increase in HBV DNA</td>
<td>3-5 fold increase of ALT above baseline (HBV flare)</td>
</tr>
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</table>

**Risk of Reactivation:**

<table>
<thead>
<tr>
<th>Risk</th>
<th>HBV serology</th>
<th>IMS</th>
</tr>
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<tbody>
<tr>
<td>Very high (&gt;20%)</td>
<td>HBsAg+</td>
<td>Anti-CD20 bst</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Undergoing HSCT</td>
</tr>
<tr>
<td>High (10-20%)</td>
<td>HBsAg+</td>
<td>High dose steroids *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-CD2 therapy</td>
</tr>
<tr>
<td>Moderate (1-10%)</td>
<td>HBsAg+</td>
<td>Chemotherapy w/o glucocorticoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-TNF therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anti-rejection therapy for SOT</td>
</tr>
<tr>
<td>Low risk (&lt;1%)</td>
<td>HBsAg+</td>
<td>Anti-CD20 therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Undergoing HSCT</td>
</tr>
<tr>
<td>Very low risk</td>
<td>HBsAg+</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td>Anti-CD2 therapy</td>
<td>Anti-TNF therapy</td>
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<td></td>
<td>Methotrexate</td>
<td>Azathioprine</td>
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* ≥ 20 mg/day for at least 4 weeks

**Treatment to Prevent HBV Reactivation in High Risk Patients:**
- Antiviral therapy be initiated concurrently or prior to immunosuppressive therapy
  - Most experience with preventive therapy has been with lamivudine
  - Tenofovir and entecavir preferred?
- Treatment duration:
  - At least 6 months after withdrawal of IMS (except anti-CD20 therapy)
  - At least 12 months after stopping anti-CD20
    - Lag in recovery of B cell function among these patients
  - Might consider long-term antiviral therapy for patients who have undergone HSCT or SOT since they often remain on chronic IMS
**HEPATITIS A:**
- RNA virus, 4 human subtypes
- Spread via fecal-oral route
  - Can occur sporadically or in an epidemic form
- Incubation period average 28-30 days
  - Maximum infectivity in latter half of incubation period to few days after onset of jaundice (communicability)

**CLINICAL PRESENTATION:**
- Injury to liver is secondary to host’s immune response
- Prodromal symptoms: fatigue, N/V, anorexia, RUQ pain
- Most common findings: jaundice and hepatomegaly (70-80% of cases)
- Marked elevation of ALT (higher than AST) usually > 1000
  - Pecedes bilirubin elevation

**DIAGNOSIS:**
- Positive HAV IgM antibodies
- HAV IgG antibodies are evidence of previous exposure or vaccination

**TREATMENT AND PREVENTION:**
- Treatment is supportive and prognosis is good
- Recovery by 3 months (up to 6 months)
- Fatalities are rare (0.1% infants, 0.4% young adults, 1.1% > 40 yrs old)
- Prevention by hand washing, avoidance of water and foods from endemic areas, vaccination
  - Prevention is key = vaccination

**HEPATITIS A AND B VACCINE:**
- 2 single-antigen inactivated hepatitis A vaccines HAVRIX & VAQTA
  - Two doses q6-12 months
  - Comparable immunogenicity, fewer side effects
- Combo inactivated vaccine, TWINRIX contains both hepatitis A (HAVRIX) and hepatitis-B (Engerix-B)
  - 3 doses (0, 1 and 6 months)
  - Well-tolerated and highly immunogenic