A Makeover for Hepatitis B

Faculty
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In November of 2017 HEPLISAV-B was approved for the prevention of hepatitis B. HePLISAV-B is a two-dose vaccine administered 4 weeks apart. It will be important for health care providers to be aware of these new options. Health care providers will need to understand how HEPLISAV-B compares to other commercially available hepatitis B vaccines. In addition, numerous limitations exist with the oral antiviral medications currently used to treat patients chronically infected with hepatitis B. New research is promising that we will have new oral antiviral therapies in the next 5 years. We will review the limitations with the current treatments and discuss agents that are currently in the pipeline.

Learning Objectives

Pharmacist
1. Recognize the epidemiology of hepatitis B
2. Compare and contrast commercially available hepatitis B vaccines
3. Identify limitations with current oral antiviral medications to treat hepatitis B

Pharmacy Technician
1. Recognize the epidemiology of hepatitis B
2. Compare and contrast the schedules for commercially available hepatitis B vaccines
3. List oral antiviral medications used to treat hepatitis B

Nurse
1. Recognize the epidemiology of hepatitis B
2. Compare and contrast commercially available hepatitis B vaccines
3. Identify limitations with current oral antiviral medications to treat hepatitis B
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Target Audience
Pharmacists, Pharmacy Technicians, Nurses

Universal Activity Number

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<th>Activity Release Date</th>
<th>Activity Offline Date</th>
<th>ACPE Expiration Date</th>
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<td>Pharmacist</td>
<td>April 24, 2019</td>
<td>April 24, 2022</td>
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<td>Pharmacy Technician</td>
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<td>Nurse</td>
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Credit Hours
1.0 Hour

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A MAKEOVER FOR HEPATITIS B

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OBJECTIVES

- Describe the epidemiology of hepatitis B
- Compare and contrast commercially available hepatitis B vaccines
- Identify limitations with current oral medications to treat hepatitis B

VIRAL HEPATITIS OVERVIEW

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus family</td>
<td>Picornaviridae</td>
<td>Hepadnaviridae</td>
<td>Flaviridae</td>
<td>Deltaviridae</td>
<td>Caliciviridae</td>
</tr>
<tr>
<td>Nucleic Acid</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Incubation period (days)</td>
<td>15-50</td>
<td>28-160</td>
<td>14-160</td>
<td>Variable</td>
<td>15-45</td>
</tr>
<tr>
<td>Mode of transmission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fecal-oral</td>
<td>Yes</td>
<td>Possible</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sexual</td>
<td>Yes</td>
<td>Yes</td>
<td>Rare</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blood</td>
<td>Rare</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cirrhosis and HCC</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>With Hep B</td>
<td>No</td>
</tr>
</tbody>
</table>
CLINICAL FORMS OF VIRAL HEPATITIS

Acute:
• Usually self-limiting
• Low mortality rate, but high morbidity
• Duration ≤ 6 months

Chronic:
• Continuation of hepatic necro-inflammatory process
• Duration ≥ 6 months

DIAGNOSIS OF ACUTE HEPATITIS B

Clinical Description
• Discrete onset of symptoms (fever, headache, malaise, anorexia, N/V/D, abdominal pain)
AND
• Jaundice OR elevated serum alanine aminotransferase (ALT) > 100 IU/L

Laboratory Criteria
• Hepatitis B surface antigen (HBsAg) positive
AND
• Immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM anti-HBc) positive

ACUTE HEPATITIS B

1991-
Routine vaccination of children recommended

1995-
Routine catch up vaccination of adolescents recommended

INCIDENCE OF ACUTE HEPATITIS B, BY AGE GROUP, 2001-2016


A Makeover for Hepatitis B
INCIDENCE OF ACUTE HEPATITIS B, BY SEX, 2001-2016

INCIDENCE OF ACUTE HEPATITIS B, BY RACE/ETHNICITY, 2001-16
CHRONIC HEPATITIS B EPIDEMIOLOGY IN THE US

- In 2016, 14,847 cases were reported to the CDC
- Prevalence estimates from 2011-12 indicated a total of 847,000 persons were living with HBV infection

INTERNATIONAL HEPATITIS B PREVALENCE
## Hepatitis B Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age Group</th>
<th>Volume</th>
<th>Route of Administration</th>
<th>Doses</th>
<th>Dosing Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engerix-B</td>
<td>0 to 19 years</td>
<td>0.5 mL</td>
<td>IM</td>
<td>3</td>
<td>Birth, 1-2 mos, 4 mos, 6-18 mos</td>
</tr>
<tr>
<td></td>
<td>≥ 20 years</td>
<td>1 mL</td>
<td></td>
<td></td>
<td>0, 1-2, 4-6 mos</td>
</tr>
<tr>
<td>Recombivax HB</td>
<td>0 to 19 years</td>
<td>0.5 mL</td>
<td>IM</td>
<td>3</td>
<td>Birth, 1-2 mos, 4 mos, 6-18 mos</td>
</tr>
<tr>
<td></td>
<td>11 to 15 years</td>
<td>1 mL</td>
<td></td>
<td>2</td>
<td>0, 4-6 mos</td>
</tr>
<tr>
<td></td>
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<td>1 mL</td>
<td></td>
<td>3</td>
<td>0, 1-2, 4-6 mos</td>
</tr>
<tr>
<td>Heplisav-B</td>
<td>≥ 18 years</td>
<td>0.5 mL</td>
<td>IM</td>
<td>2</td>
<td>0, 1 mo</td>
</tr>
<tr>
<td>Pediarix DTaP + Hep B + IPV</td>
<td>6 weeks to 6 years</td>
<td>0.5 mL</td>
<td>IM</td>
<td>3</td>
<td>Birth, 2 mo, 4 mo, 6 mos</td>
</tr>
<tr>
<td>Twinrix HepA + HepB</td>
<td>≥ 18 years</td>
<td>1 mL</td>
<td>IM</td>
<td></td>
<td>0, 1, 6 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>0, 7, 21-30 days, 12 mos</td>
</tr>
</tbody>
</table>

HEPLISAV-B

A Makeover for Hepatitis B
WHY THE NEED FOR AN ADDITIONAL HEPATITIS B VACCINE?

BARRIERS TO HBV VACCINATION IN THE ADULT POPULATION

- Immunogenic hypo-responsiveness
- Adherence with dosing schedule
- Extended time to develop sero-protective levels of antibodies
IMMUNOGENICITY AND SAFETY OF AN INVESTIGATIONAL HEPATITIS B VACCINE WITH A TOLL-LIKE RECEPTOR 9 AGONIST ADJUVANT COMPARED TO A LICENSED HEPATITIS B VACCINE IN HEALTHY ADULTS 40-70 YEARS OF AGE


METHODS

• Phase 3, multicenter, randomized, subject- and observer-blinded, active controlled trial in healthy subjects aged 40-70 years
• Primary objective: non-inferiority of the sero-protection rate at 8 weeks following the last dose of the vaccine
• Secondary objectives: comparison of safety profiles and superiority of the immune response of HBsAg-1018 if non-inferiority was established
STUDY POPULATION AND DOSING

• Inclusion criteria: adults ages 40-70 years, seronegative for HBsAg, anti-HBs, antibody against hepatitis B core antigen and HIV
• Exclusion: pregnant, breastfeeding, planning to become pregnant, history of HBV infection or autoimmune disease, previously received any hepatitis B vaccine
• All subjects received 3 intramuscular injections at 0, 4 and 24 weeks

RESULTS

• 2,452 patients randomized
• 51.9% female
• Mean age: 54 years
• Efficacy (seroprotective rates):
  • HBsAg-1018: 90%
  • HbsAg-Eng: 70.5%
• Safety:
  • Local reactions: ~30% in both groups
  • Systemic reactions: ~30% in both groups
IMMUNOGENICITY AND SAFETY OF AN INVESTIGATIONAL HEPATITIS B VACCINE WITH A TOLL-LIKE RECEPTOR 9 AGONIST ADJUVANT (HBSAG-1018) COMPARED WITH A LICENSED HEPATITIS B VACCINE IN PATIENTS WITH CHRONIC KIDNEY DISEASE


METHODS

• Phase 3 multicenter, randomized, observer-blinded, active controlled trial in patients ages 18-75 years with CKD
• Primary objective: non-inferiority of the sero-protection rate at 4 weeks following the last dose of the vaccine
• Secondary objectives: comparison of safety profiles and superiority of the immune response of HBsAg-1018 if non-inferiority was established
STUDY POPULATION AND DOSING

• Inclusion criteria: 18-75 years with CKD (eGFR ≤ 45 mL/min), seronegative for HBsAg, anti-HBs, antibody against hepatitis B core antigen and HIV and not scheduled to undergo kidney transplant within the next 12 months

• Exclusion: pregnant, breastfeeding, planning to become pregnant, history of HBV, HCV or HIV infection or autoimmune disease, previously received any hepatitis B vaccine, receiving chemotherapy, uncontrolled DM or HTN, received blood products or immunoglobulin within 3 months, recently received erythropoietin, IV iron, immunosuppressive therapy or any investigational agent

• All subjects received 4 intramuscular injections at 0, 4, 8 and 24 weeks

RESULTS: DEMOGRAPHICS

• 521 patients randomized
• 38.1% female
• Mean age: 61.3 years
• White: 78.7%
• Hemodialysis: 13.8%
• Type 2 DM: 64.7%
• Hypertension: 97.2%
RESULTS: EFFICACY AND SAFETY

Efficacy (seroprotective rates):
• HBsAg-1018: 89.9%
• HbsAg-Eng: 81.8%

Safety:
• Local reactions: ~30% in both groups
• Systemic reactions: ~30% in both groups

HEPATITIS B VACCINES

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age Group</th>
<th>Volume</th>
<th>Route of Administration</th>
<th>Doses</th>
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<td>0, 4-6 mos</td>
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<td>2</td>
<td>0, 1 mo</td>
</tr>
</tbody>
</table>
ACIP RECOMMENDATIONS

- Heplisav-B may be used as a HepB vaccine in persons ≥ 18 years recommended for vaccination against HBV
- Persons at risk for infection through sexual exposure
- Persons with a history of current or recent drug use
- Persons at risk for infection by percutaneous or mucosal exposure to blood
- International travelers to countries with high or intermediate levels of endemic HBV infection
- Persons with HCV infection or other chronic liver disease
- Persons with HIV
- Incarcerated persons
HEPATITIS B

Transmission:
- Percutaneous
- Permucosal

Signs and Symptoms:
- Fever
- Fatigue
- Loss of appetite
- Nausea/ vomiting
- Abdominal pain
- Dark urine
- Jaundice

ACUTE HEPATITIS B: TREATMENT

- Usually not necessary
- >95% of immunocompetent adults recover spontaneously
- Treatment for patients with fulminant hepatitis B
HIGH RISK POPULATIONS WHO SHOULD RECEIVE SCREENING

- Persons born in regions of high or intermediate HBV endemicity
- Persons who have ever injected drugs
- Men who have sex with men
- Persons needing immunosuppressive therapy
- Individuals with elevated ALT or AST of unknown etiology
- Persons with ESRD
- Unvaccinated persons with DM age 19 through 59
- Pregnant women
- Persons with chronic liver disease (HCV)
- Persons with HIV

HEPATITIS B: SEROLOGIES

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>Anti-HBc</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Immune, via natural infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Immune, via vaccination</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Acute infection</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Resolved infection, false positive anti HBC, “low level” chronic infection, resolving acute infection</td>
</tr>
</tbody>
</table>

http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm
HEPATITIS: HBEAG STATUS

- Product of the nucleocapsid gene
- Indicates viral replication
- Absent in “precore mutant” HBV

http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm

DIAGNOSIS OF CHRONIC HEPATITIS B

Clinical Description
- No symptoms required
- May have no evidence of liver disease

Laboratory Criteria
- IgM to IgM anti-HBc negative
  AND
  - Positive HBsAg
  - HBeAg
  - HBV DNA positive
- OR
  - HBsAg positive or HBV DNA positive or HBeAg positive two times when tested 6 months apart
### PHASES OF CHRONIC HEPATITIS B INFECTION

<table>
<thead>
<tr>
<th>Phase</th>
<th>ALT</th>
<th>HBV DNA</th>
<th>HBeAg</th>
<th>Liver Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune-tolerant phase</td>
<td>Normal</td>
<td>Elevated, typically &gt; 1 million IU/mL</td>
<td>Positive</td>
<td>Minimal inflammation and fibrosis</td>
</tr>
<tr>
<td>HBeAg-positive immune-active phase</td>
<td>Elevated</td>
<td>Elevated ≥ 20,000 IU/mL</td>
<td>Positive</td>
<td>Moderate-to-severe inflammation or fibrosis</td>
</tr>
<tr>
<td>Inactive phase</td>
<td>Normal</td>
<td>Low or undetectable &lt; 2,000 IU/mL</td>
<td>Negative</td>
<td>Minimal necroinflammation but variable fibrosis</td>
</tr>
<tr>
<td>HBeAg-negative immune reactivation phase</td>
<td>Elevated</td>
<td>Elevated ≥ 2,000 IU/mL</td>
<td>Negative</td>
<td>Moderate-to-severe inflammation or fibrosis</td>
</tr>
</tbody>
</table>

### HEPATITIS B: COMPLICATIONS

**Risk factors for disease progression:**
- Immune compromised
- Male gender
- Advanced age
- HBV DNA levels > $10^4$ copies/mL
- Elevated ALT
- Concurrent infections
- EtOH consumption
- Metabolic syndrome

**Complications:**
- Hepatocellular carcinoma (HCC)
- Cirrhosis
- Hepatic failure
ALGORITHM TO DETERMINE NEED FOR TREATMENT

HBeAg Positive

- HBV DNA > 20,000 IU/mL
  - Elevated ALT
    - Treat
  - Normal ALT
    - Monitor ALT every 3 months x 1 year
      - Consider liver biopsy if > 40 Significant fibrosis or inflammation

HBeAg Negative

- HBV DNA > 2,000 IU/mL
  - Elevated ALT
    - Monitor ALT every 3 months x 1 year
  - Normal ALT
    - Consider liver biopsy if > 40 Significant fibrosis or inflammation

Goals of Therapy:
- Suppress viral replication
- Prevention of complications

Assessing Response:
- ALT normalization
- Decreased serum HBV DNA level
- Loss of HBeAg +/- anti-Hbe
- Improved liver histology
Currently FDA Approved:
• Pegylated interferon- α-a2
• Lamivudine
• Adefovir
• Entecavir
• Telbivudine
• Tenofovir

Active studies:
• Emtricitabine
• Pradofovir
• Clevudine

Dosing: 180 mcg subcutaneously once weekly

Monitoring:
• ALT (every 3 months)
• CBC
• TSH
• HBV DNA (every 3-6 months)

Adverse effects:
• Influenza-like illness
• Fatigue
• Anorexia
• Weight loss
• Bone marrow suppression
• Depression
• Thyroiditis
CHRONIC HEPATITIS B: ENTECAVIR

Dosing:
- Treatment naïve: 0.5 mg PO daily
- Treatment experienced: 1 mg PO daily
- Renal dysfunction requires dose adjustment

Adverse effects:
- Headache
- Fatigue
- Dizziness
- Nausea

Monitoring:
- LFTs (every 3 months)
- HBV DNA (every 3-6 months)

CHRONIC HEPATITIS B: TENOFOVIR

Dosing:
- Tenofovir disoproxil fumarate (Viread): 300 mg PO daily
  - Adjust dose in renal dysfunction
- Tenofovir alafenamide (Vemlidy): 25 mg PO daily
  - Not recommended in CrCl < 15 mL/min

Adverse effects:
- Fanconi syndrome
- Renal insufficiency

Monitoring:
- LFTs (every 3 months)
- HBV DNA (every 3-6 months)
CHRONIC HEPATITIS B: THERAPY DURATION

HBeAg-positive patients:
- 12 months past achieving anti-Hbe
- Or until HBsAg loss

HBeAg-negative patients:
- Indefinite
- Consider if HBsAg clearance occurs

SUMMARY

- The prevalence of hepatitis B has decreased significantly since HBV vaccination was added to the pediatric dosing schedule
- Adults are less likely to develop chronic hepatitis B infection
  - Can have significant morbidity and mortality when infection becomes chronic
- The newest HBV vaccine may address some barriers with vaccination including:
  - Difficulty adhering to the dosing schedule
  - Decreased immunologic response
SUMMARY

• HBV therapies can help decrease the morbidity and mortality associated with chronic infection
  • Not currently able to cure the disease
  • Significant controversy exists regarding discontinuation