LIVER DISEASE AND TREATMENT: VIRAL HEPATITIS

Van Hilburn, Pharm.D., MBA

OBJECTIVES
- Review the pathophysiology and clinical course of viral hepatitis
- Discuss the role of vaccination and immunoglobulins in the prevention of viral hepatitis.
- Describe the therapeutic management of viral hepatitis.
- Discuss the economic impact and epidemiology of viral hepatitis.

OVERVIEW OF THE LIVER
- The largest and most important organ
- Average-size of liver is of a 3 pound football
- Function is to filter and detoxify the blood
- The liver is storage and chemical factory
LIVER DISEASE

• Causes of liver damage
  – Viruses
  – Heavy alcohol consumption
  – Obesity
  – Drug induced
  – Exposures to chemicals

VIRAL HEPATITIS

• Definition
  – Inflammation of the liver caused by infection by at least 5 distinct viruses.

• Most common types
  – Hepatitis A virus (HAV)
  – Hepatitis B virus (HBV)
  – Hepatitis C virus (HCV)

• Less common types
  – Hepatitis D virus (HDV)
  – Hepatitis E virus (HEV)

VIRAL HEPATITIS

• Leading cause of liver cancer.
• Most common reason for liver transplantation.
• Estimated 4.4 million Americans living with chronic hepatitis.
• Majority of Americans do not know they are infected.
REPORTED CASES OF ACUTE VIRAL HEPATITIS 1993-2003

VIRAL HEPATITIS

- Clinical Presentation
  - Acute
    - Presents in Hepatitis A, B, and C.
  - Fulminant (Acute Liver Failure)
    - Hepatitis A – occasionally
    - Hepatitis B – 1%
    - Hepatitis C – rare
  - Chronic
    - Hepatitis B
    - Hepatitis C

HEPATITIS A VIRUS
HEPATITIS A VIRUS

- Epidemiology and Etiology
  - Transmitted through the fecal-oral route.
  - Spreads primarily through close contact.
  - Most frequently reported disease in the United States.
  - Hepatitis A virus vaccine has been available in the United States since 1995.

HEPATITIS A OUTBREAKS

HEPATITIS A VIRUS

- Risk Factors
  - International travelers
  - Sexual intercourse
  - IV and non-IV drug users
  - Children living in communities
HEPATITIS A VIRUS

3 Stages of Infection

- Incubation period (~28 days)
  - Begins shortly after oral or parenteral inoculation
  - Antigens shed into bile and feces
  - Highest peak infectivity at this time
- Acute Hepatitis
  - Preicteric phase (before jaundice)
  - Icteric hepatitis
- Convalescence
  - Complete recovery

PRESENTATION

- Preicteric phase
  - Nausea
  - Anorexia
  - Fever
  - Malaise
  - Abdominal pain
- Icteric phase
  - Jaundice
  - Elevated ALT/AST

LABORATORY TESTS

- Positive IgM anti-HAV
- Mild elevations
  - Serum bilirubin
  - γ-globulin
  - ALT/AST

TREATMENT

- Supportive care
  - Healthy diet
  - Rest
  - Maintaining fluid balance
  - Avoid
  - Hepatotoxic drugs
  - Alcohol

PREVENTION

- Good hygiene
  - Hand washing
  - Bathroom
  - Diaper changes
  - Food prep

- Good hygiene
  - Hand washing
  - Bathroom
  - Diaper changes
  - Food prep
HEPATITIS A VIRUS

- Pharmacological treatment
  - Immunoglobulin to prevent Hepatitis A
    - Hepatitis A immunoglobulin
      - 85% effective in preventing spread
  - Vaccines to Prevent Hepatitis A
    - Havrix
    - Vaqta
    - Twinrix

- Who should get vaccinated
  - All children at age 1 year
  - Children and adolescents ages 2-18 in communities with a high disease incidence
  - Persons traveling to or working in countries with high or intermediate rates of hepatitis A
  - Men who have sex with men
  - Illegal drug users: IV and non-IV
  - Occupational risk
  - Chronic liver disease
  - Clotting disorders

HEPATITIS A

**INDICATION** | **DOSE**
--- | ---
Pre-exposure travel | Pre-exposure
- Travel within 1 month | Travel < 3 months: 0.02 ml/kg IM
- Age under 1 year | Travel > 3 months: 0.06 ml/kg IM
- Institutional workers | (within 2 weeks)
HEPATITIS A

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>USAGE</th>
<th>ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVRX Hepatitis A</td>
<td>≥ 12 months</td>
<td>Primary dose should be given at least 2 weeks prior to expected exposure</td>
</tr>
<tr>
<td>VAQTA Hepatitis A</td>
<td>≥ 12 months</td>
<td>Primary dose should be given at least 2 weeks prior to expected exposure</td>
</tr>
<tr>
<td>TWINRIX Hepatitis A, Hepatitis B</td>
<td>18 years of age or older</td>
<td>Std: 3 doses at 0, 1, &amp; 6 mo</td>
</tr>
</tbody>
</table>

VAQTA Hepatitis A

- Primary dose should be given at least 2 weeks prior to expected exposure
- Children/adolescents: 0.5 ml M-dose and 0.5 ml booster dose 6 to 12 months later
- Adults: 1 ml M-dose and 1-ml booster 6 to 12 months later

TWINRIX Hepatitis A, Hepatitis B

- Primary dose should be given at least 2 weeks prior to expected exposure
- Children/adolescents: 0.5 ml M-dose and 0.5 ml booster dose 6 to 18 months later
- Adults: 1 ml M-dose and 1-ml booster 6 to 18 months later

HEPATITIS B VIRUS

- Epidemiology and Etiology
  - Transmitted by percutaneous or mucosal exposure to infectious blood or body fluids
  - Incubation period is 6 weeks to 6 months
  - Virus can survive 7 days outside the body
  - In 2009, the incidence of reported acute Hepatitis B was 1.5 per 100,000 population
  - Rates are highest among male adults age 25-44
HEPATITIS B VIRUS

- Risk Factors
  - IV drug users
  - Unprotected sex
    - Multiple sex partners
    - Men who have sex with men (MSM)
  - Mother to infant transmission
  - Household contact of a person with chronic HBV
  - Adults at increased risk for infection
    - Healthcare workers
    - Dialysis patients
    - Recipients of certain blood products

HEPATITIS B VIRUS

ACUTE HEPATITIS B
- (+) anti-HBc IgM
- Patient is infectious
- Incubation dependent on age: 6 to 24 weeks
- Asymptomatic
  - Infants
  - Children 1 to 5 yrs old

SYMPTOMS
- Fever
- Anorexia
- Nausea
- Vomiting
- Jaundice
- Dark urine
- Clay-colored stools
- Abdominal pain

HEPATITIS B VIRUS

CHRONIC HEPATITIS B
- (+) HBsAg for at least 6 months OR
- (+) HBsAg AND anti-HBc IgM
- ALT/AST and hepatitis B virus DNA > 10^5
- Developing HBV inversely related to age
- Patient is infectious

SYMPTOMS
- Fatigue and anxiety
- Anorexia and malaise
- Ascites
- Jaundice
- Variceal bleeding
- Hepatic encephalopathy
- Vomiting and seizures
HEPATITIS B VIRUS - OUTCOMES

ACUTE HEPATITIS B
- Management
  - No specific therapy
- Development of fulminant hepatitis
  - Supportive care

CHRONIC HEPATITIS B
- Short-term
  - Limit hepatic inflammation
  - Reduce risk of fibrosis and/or decompensation
  - Eradicate/permanently suppress HBV
- Prevent long-term complications
  - Cirrhosis
  - Liver failure
  - HCC

HEPATITIS B VIRUS - PREVENTION
- Universal vaccination of infants beginning at birth
- Prevention of perinatal HBV infection through routine screening
  - Immunoprophylaxis to infants
- Routine vaccination of previously unvaccinated children and adolescents
- Vaccination of adults at increased risk for infection

VACCINATION
- Single-antigen
  - ENGERIX-B
  - RECOMBIVAX HB
- Combination
  - COMVAX
  - PEDIARIX
  - TWINRIX

HEPATITIS B VIRUS - VACCINATION SCHEDULE

<table>
<thead>
<tr>
<th>Age Group</th>
<th>RECOMBIVAX HB</th>
<th>ENGEBIX-B</th>
</tr>
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<tbody>
<tr>
<td>Infants (&lt;1 yr)</td>
<td>0.5 ml</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>Children (1-10 yrs)</td>
<td>0.5 ml</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>Adolescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-15 yrs</td>
<td>1 ml</td>
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<td>11-19 yrs</td>
<td>0.5 ml</td>
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<tr>
<td>Adults (≥20 yrs)</td>
<td>1 ml</td>
<td>1 ml</td>
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<tr>
<td>Hemodialysis patients/immunocompromised</td>
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<td>18 yrs</td>
<td>0.5 ml</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>&gt; 20 yrs</td>
<td>1 ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>General vaccination schedule: 3 IM injections at 0, 1 and 6 months</td>
<td></td>
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HEPATITIS B VIRUS

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<tr>
<th>COMBINATION VACCINE</th>
<th>COMVA X</th>
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<th>TWINRIX</th>
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CHRONIC HEPATITIS B VIRUS

INTERFERONS
- Intron A
  - (interferon alpha-2b)
- Pegasy
  - Pegylated interferon

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
- NRTIs
  - Adefovir (Hepsera)
  - Entecavir (Baraclude)
  - Lamivudine (Epivir-HBV)
  - Telbivudine (Tyzeka)
  - Tenofovir (Viread)

SIDE EFFECTS
- Flu-like symptoms
- Mood swings, depression, and anxiety
- Hypothyroidism
- Bone marrow suppression
- Infection
- Hair loss

CHRONIC HEPATITIS B VIRUS

INTERFERON
- Naturally occurring protein made by white blood cells that combats viral infections
- Stimulates body’s immune system to clear the virus
CHRONIC HEPATITIS B VIRUS

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<th>GENERIC NAME</th>
<th>DOSE</th>
<th>INDICATION</th>
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<tbody>
<tr>
<td>Intron A</td>
<td>Interferon- alph 2b</td>
<td>5 million IU IM/SUBQ daily or 10 million IU 3/week for 16 weeks or 48 weeks for HBeAg (-)</td>
<td>Chronic HBV Compensated liver disease</td>
</tr>
<tr>
<td>Pegasis</td>
<td>Pegylated interferon</td>
<td>180 mcg SUBQ QWK for 48 weeks</td>
<td>Chronic HBV Compensated liver disease</td>
</tr>
</tbody>
</table>

NRTIs

- Used to slow the ability of hepatitis B virus from multiplying
- Duration of therapy for at least a year or longer
- Success is if virus is not longer multiplying, liver enzymes return to normal, and liver damage improves
- Relapse is common

SIDE EFFECTS

- Fever
- Feeling tired or weak
- Headache
- Sore throat
- Diarrhea
- Dizziness
- Pain in your belly/back

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<tr>
<td>Baraclude</td>
<td>Entecavir</td>
<td>0.5 mg – 1 mg daily</td>
<td>chronic HBV viral replication</td>
</tr>
<tr>
<td>Epivir- HBV</td>
<td>Lamivudine</td>
<td>100 mg daily</td>
<td>chronic HBV viral replication liver inflammation</td>
</tr>
<tr>
<td>Hepsera</td>
<td>Adefovir dipivoxil</td>
<td>10 mg daily</td>
<td>chronic HBV in patients &gt; 12 yrs</td>
</tr>
<tr>
<td>Tyzeka</td>
<td>Tenofovir</td>
<td>600 mg daily</td>
<td>chronic HBV Viral replication Elevated ALT/AST</td>
</tr>
<tr>
<td>Viread</td>
<td>Tenofovir</td>
<td>300 mg daily</td>
<td>Chronic HBV</td>
</tr>
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HEPATITIS C VIRUS

1.3% of the population are infected with HCV

4% of veterans who use the Department of Veterans Affairs have HCV

Chronic HCV

- Cirrhosis
- Hepatocellular carcinoma
- End stage liver disease requiring liver transplantation

Most common chronic blood borne infection

Transmitted through percutaneous or mucosal exposure

- IV drug use
- Sexual intercourse

Estimated 3.2 million chronically infected

70% of newly infected persons are asymptomatic.

Currently no vaccine against HCV infection
## Acute Hepatitis C

**Signs and Symptoms**
- Acute viral hepatitis
  - Anorexia
  - Abdominal discomfort
  - Nausea
  - Vomiting
  - Jaundice/dark urine or
  - ALT levels >400 IU/L

**Diagnosis**
- One or more of the following
  - Positive anti-HCV OR
  - HCV RIBA OR
  - Positive NAT: HCV RNA
- And the following two:
  - Negative IgM anti-HAV
  - Negative IgM anti-HBc

## Chronic Hepatitis C

**Signs and Symptoms**
- Asymptomatic
- Chronic liver disease
  - Cirrhosis
    - Scarring called fibrosis that causes the liver to shrink & become hard
    - Compensated: no symptoms
    - Decompensated
  - Liver cancer
  - Liver transplant

**Diagnosis**
- Positive anti-HCV
  - Positive HCV RIBA
  - Positive NAT for HCV RNA
  - HCV genotype

## Hepatitis C Virus

- 6 Genotypes of hepatitis C
- Common 3 genotypes in the United States
  - Genotype 1a or 1b
    - More “resistant” to treatment
    - 72% of Americans
  - Genotype 2a or 2b
    - Sensitive to treatment
    - 10% of Americans
  - Genotype 3a or 3b
    - Sensitive to treatment
    - 6% of Americans
HEPATITIS C VIRUS

• EPIDEMIOLOGY AND ETIOLOGY
  – HCV RNA detected in blood within 1 to 3 months
  – Anti-HCV can be detected in >97% by 6 months after exposure
  – Chronic HCV infection
    • Develops in 70% - 85% of HCV infected persons
    • 60% - 70% of persons infected with HCV have active liver disease

• PRESENTATION
  • Nausea
  • Anorexia
  • Fever
  • Malaise
  • Abdominal pain
  • Jaundice
  • Alanine > 400 IU/L

• DIAGNOSIS
  • IgM anti-HAV negative, and
  • IgM anti-HBc negative, and
  • One of the following
    – Anti-HCV positive, OR
    – HCV RIBA positive, OR
    – Nucleic acid test (NAT) for HCV RNA positive

• Prevention
  – Screening and testing of blood donors
  – Viral inactivation of plasma-derived products
  – Risk-reduction counseling and screening of persons at risk for HCV infection
  – Routine practice of infection control in health-care settings
**HEPATITIS C VIRUS**

- **Watchful waiting and Life style modification**
  - Healthy diet
  - Avoiding alcohol

- **Goal watchful waiting**
  - Monitor progression of disease/natural disease
  - Keeping patients feeling well

- **Candidates for watchful waiting**
  - Mild liver disease
  - Patients with high risk factors
  - New treatment

<table>
<thead>
<tr>
<th>Goal of drug treatment</th>
<th>Does not occur in all patients</th>
<th>Stop or slow down the liver damage</th>
<th>Reduce risk of cirrhosis</th>
<th>Treatment can:</th>
<th>Slow scarring and damage to the liver</th>
<th>Decrease the amount of hepatitis C virus and ALT</th>
<th>Improve quality of life</th>
<th>Reduce effect of HCV on kidneys and skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanently remove/clear HCV from body</td>
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CHRONIC HEPATITIS C VIRUS

- Drug treatment recommended in patients if:
  - Damage found in liver biopsy
  - Patients who are motivated to undergo treatment
  - Patients who are compliant with necessary tests and visits
  - Patients infected within the past 6 months with acute hepatitis C virus
  - Patients who are coinfected with HIV or hepatitis B

CHRONIC HEPATITIS C VIRUS

- Drug treatment
  - Pegylated Interferon
    - Pegylated interferon alfa-2a
    - Pegylated interferon alfa-2b
    - Given as 1 shot a week
  - Ribavirin
  - Standard interferon
    - Rarely used
    - Given as 3 shots a week
  - Combination therapy
    - Pegylated interferon and ribavirin

HEPATITIS C VIRUS

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>- Insomnia</th>
<th>- Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Short-tempered</td>
<td>- Depression</td>
</tr>
<tr>
<td></td>
<td>- Fatigue</td>
<td>- Headaches</td>
</tr>
<tr>
<td></td>
<td>- Fever</td>
<td>- Muscle and body aches</td>
</tr>
<tr>
<td></td>
<td>- Poor appetite</td>
<td>- Bad taste in mouth</td>
</tr>
<tr>
<td></td>
<td>- Dry mouth/tick saliva</td>
<td>- Sore mouth/sore throat</td>
</tr>
<tr>
<td></td>
<td>- Nausea and vomiting</td>
<td>- Diarrhea</td>
</tr>
<tr>
<td></td>
<td>- Hair loss</td>
<td>- Skin rash</td>
</tr>
<tr>
<td></td>
<td>- Injection site reaction</td>
<td>- Chest pain</td>
</tr>
<tr>
<td></td>
<td>- Shortness of breath</td>
<td>- Vision changes</td>
</tr>
<tr>
<td></td>
<td>- Thyroid problems</td>
<td>- Low red blood cells</td>
</tr>
<tr>
<td></td>
<td>- Low white blood cells</td>
<td>- Low platelets</td>
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</tbody>
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### CHRONIC HEPATITIS C VIRUS

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<th>DOSE</th>
<th>INDICATION</th>
</tr>
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<tbody>
<tr>
<td>Incivek</td>
<td>Telaprevir</td>
<td>750 mg TID for 12 weeks</td>
<td>HCV genotype 1 with peginterferon alfa and ribavirin</td>
</tr>
<tr>
<td>Victrelis</td>
<td>Boceprevir</td>
<td>400 mg TID for 4 weeks</td>
<td>HCV genotype 1 with peginterferon alfa and ribavirin</td>
</tr>
<tr>
<td>CoPegasus</td>
<td>Ribavirin</td>
<td>400 mg to 1400 mg BID</td>
<td>Combination with peginterferon or roferon</td>
</tr>
<tr>
<td>Rebetol</td>
<td>Ribavirin</td>
<td>400 mg to 1400 mg BID</td>
<td>Combination with interferon alfa-2b</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>Pegasys</td>
<td>Pegylated interferon</td>
<td>180 mcg once weekly</td>
<td>Monotherapy or in combo with ribavirin</td>
</tr>
<tr>
<td>Pegintron</td>
<td>Pegylated interferon alfa-2b</td>
<td>1 mcg/kg/SC</td>
<td>In combination with ribavirin</td>
</tr>
<tr>
<td>Intron A</td>
<td>Interferon alfa-2b</td>
<td>1 to 1.5 mcg/kg/SC</td>
<td>In combination with ribavirin</td>
</tr>
<tr>
<td>Roferon</td>
<td>Interferon alfa 2a</td>
<td>3 million IU SC TID for 12 wks</td>
<td>HCV in patients 18 years or older</td>
</tr>
<tr>
<td>Intergen</td>
<td>Interferon aphacom-1</td>
<td>15 mcg/dose SC</td>
<td>18 yrs with anti-HCV serum antibodies</td>
</tr>
</tbody>
</table>

### REFERENCES

- http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm101494.htm